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PROCEEDINGS

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Section of Medicine

President—Sir ALUN ROWLANDS, K.B.E., M.D., F.R.C.P.

[*March* 24, 1953]

DISCUSSION ON THE CHEMOTHERAPY OF THE RETICULOSES

Dr. John F. Wilkinson: I propose to consider the treatment of Hodgkin's disease, the leukæmias, and those other less frequently seen reticuloses, some of which are closely related to or may even be manifestations of certain acute leukæmias. It is most disturbing to note the increasing frequency of these conditions during the last twenty years or so.

Thus, from the Registrar-General's statistics the deaths from Hodgkin's disease have shown a slowly progressive increase in frequency, for example, from 566 (367 males and 199 females) in 1940 to 663 (414 males and 249 females) in 1950. There have been similar increases in the death-rates of other reticuloses, but the most disquieting of all has been the death-rate for the leukæmias which has increased from a total of 446 in 1921 to 1,832 in 1950. This is the common experience of all who see large numbers of these cases in their clinics, and it is certainly not due to more accurate diagnoses.

My chemotherapeutic investigations were carried out on 420 patients with acute or chronic leukæmias, Hodgkin's disease, or other forms of reticuloses.

Chemotherapeutic Agents

Apart from the earlier pre-war trials of arsenic, benzene, and similar substances, the present-day chemotherapeutic treatment of the reticuloses really has its origin in wartime research work which we commenced in Manchester in 1942. Originally at the request of Sir Edward Mellanby, then Secretary of the Medical Research Council, I had a small team working on and supervising the hæmatological changes occurring in workers engaged in the preparation and manufacture of chemical warfare agents of which the most interesting to us were the β-halogenated alkylamine type of vesicants popularly known as the nitrogen mustards. It was soon apparent to us that a profound depression of the leucocytes in blood and marrow was produced by exposure to these substances and led to my trying some of these β-chloro alkylamine series of agents intravenously on patients with initially high leucocyte counts (i.e. chronic leukæmias). This work was carried out at the Manchester Royal Infirmary. Chronic myeloid and lymphatic leukæmias, and later Hodgkin's disease, were found to be very sensitive to small doses of some of these agents (Wilkinson and Fletcher, 1947). Other research work has been continued actively since that time, but for reasons of security we were not able to publish the work until long after the end of the war. Many groups of workers have since confirmed my original observations.

Of all the substances tested at that time

tri-(2-chloroethyl)-amine hydrochloride ($Cl.CH_2.CH_2)_3$: N. HCl.,

and di-(2-chloroethyl)-methylamine hydrochloride ($Cl.Ch_2.CH_2)_2$: $N.(CH_3).HCl$., were found to be the most valuable for the treatment of chronic leukæmias and Hodgkin's disease, and to a lesser degree, polycythæmia and rarer forms of reticuloses.

These substances, often referred to as the nitrogen mustards, have profoundly depressant effects on the leucopoietic tissues much earlier than any effects they may have on the red cell series so that leukæmias are more easily and effectively treated than polycythæmia.

TRI-(2-CHLOROETHYL)-AMINE HYDROCHLORIDE

Dosage and Technique

These two di- and tri-(2 chloroethyl)-amines in the form of their hydrochlorides are very soluble in water, in which they rapidly undergo firstly a reversible chemical rearrangement with the formation of very reactive ethylene-imonium derivatives which produce powerful nucleotoxic and cytotoxic

effects on enzyme systems and mitosis in rapidly proliferating cells; these intermediate derivatives undergo hydrolysis in aqueous solution but especially in the presence of weak alkali, being converted to relatively inactive chlorhydrins and chlorine-free hydroxyamines having no leucotoxic activity.

For this reason, it is obvious that solutions of the nitrogen mustards must be made up freshly at the time of their administration, and not by the dispenser some hours or days before.

In spite of their vesicant properties these amines, as their hydrochlorides, can be given safely, and without fear, intravenously in diluted solution. From a very long and extensive experience of these substances I can confirm that the tri-(2-chloroethyl)-amine hydrochloride is the better and more convenient of the two amines, extremely rarely causing phlebosclerosis. The di-compound shows a greater tendency to cause local thromboses.

While the original dosage employed was 0·1–0·2 mg./kg. body weight, I have found that for an adult 6 mg. is a convenient standard single dose that can be weighed out and stored in sterile dry ampoules ready for solution in sterile water immediately before use. This dose of 6 mg. may be repeated if necessary in say two to three days or longer according to the level of the leucocyte count, which is done daily. Further doses are given when the leucocyte count ceases to fall further after the previous dose, until the required level is reached.

We find that the most convenient method of giving this treatment is to set up an intravenous saline drip with a No. 1 needle (or No. 2 in small veins), running the saline in as fast as the small needle will permit. *Then, and only then*, is the 6 mg. of tri-(2-chloroethyl)-amine hydrochloride dissolved in 5–10 ml. water and injected through the drip tube into the flowing saline, and thus run into the vein; after two to three minutes of saline flow the procedure is complete. It is also usual to give some patients 1 tablet of Phenergan or Avomine, repeating it four hours later to prevent or reduce any nausea. The majority of these treatments are given in my *out-patient* clinics.

Sensitivity to these nitrogen mustards varies quite considerably in different patients; thus a single injection of 6 mg. may be quite adequate to reduce a high leucocyte count to normal levels for many months (*see* Fig. 1 in Gardikas and Wilkinson, 1952); in another case several doses may be necessary (*see* Figs. I–IV in Wilkinson and Fletcher, 1947).

Effects of Nitrogen Mustard Therapy

The clinical effects of this treatment are local and general.

Local.—With the tri-compound no serious local effects occur but the di-compound tends occasionally to produce local tenderness and thrombosis of the veins at the site of the injection. Leakages into the tissues may cause local inflammation, pain and necrosis. These local effects are usually due to faulty techniques and should never occur if the dilute solution is given by the drip technique.

General effects may be mainly transient headaches, nausea, anorexia. Nausea and vomiting in varying degree may occur in about 20% and 12% respectively of patients coming on about two to five hours later and passing off in a few hours; only 0·1% showed a temporary and symptomless moderate neutropenia. These effects can be controlled or reduced in severity by the use of Avomine, Dramamine, or anti-histamine drugs given at the time of the injections and repeated about four hours later.

Changes produced in the blood and marrow.—The most marked changes are seen in the reduction of the leucocyte count, the most sensitive cells being the immature or rapidly growing cells in marrow and blood. Consequently the total leucocyte count begins to fall rapidly about the second to fifth day from the first injection, the maximal effect being seen about the seventh to fourteenth day, but this may be delayed or accelerated by varying the dose in patients with differing sensitivities. The immature cells may disappear completely from the blood by this time. The platelet count shows a corresponding but much less degree of reduction while the red cell count and hæmoglobin usually remain unchanged, but later rise spontaneously in the chronic leukæmias as the leucocyte count falls. Corresponding changes are noted in the bone-marrow where depression of the leucopoietic tissues is most striking and where they may return to a normal appearance. Overdoses with these nitrogen mustards will produce aplasia of marrow or agranulocytosis, but we have not seen it happen in our cases. Because of these depressant effects on the leucopoietic tissues of patients with chronic leukæmia it is important to control the treatment by regular leucocyte and platelet counts—daily in the first place until the desired count is reached, and then depending on the frequency of the treatments and clinical condition. I personally do not give any specific treatment for chronic leukæmia if the leucocyte count is less than 15,000–20,000. The leucocytes of the normal individual show a similar sensitivity to nitrogen mustards. On the other hand, in Hodgkin's disease, other reticuloses and polycythæmia vera, the leucocytes are apparently much less sensitive to these therapeutic doses of nitrogen mustard so that it is usually quite safe to give them treatment with a total leucocyte count of only 5,000 or so.

Glandular enlargement (Table I).—After nitrogen mustard therapy the splenomegaly of chronic leukæmia or Hodgkin's disease regresses rapidly while the enlarged lymph nodes of chronic lymphatic leukæmia and Hodgkin's disease may diminish extremely quickly, often in the course of seven to fourteen days, and can be kept down with appropriately spaced doses. Similarly, deposits in bones may respond almost equally quickly.

TABLE I.—RESPONSES FOLLOWING NITROGEN MUSTARD THERAPY IN 126 CASES OF CHRONIC LEUKÆMIA

Sign or symptom	No. of patients in whom symptom or sign was present before treatment		After treatment		
	Myeloid	Lymphatic	Relieved Completely	Partially	Unrelieved
Splenomegaly	70		32	34	4
		22	8	12	2
Lymphadenopathy		48	15	29	4
Fatigability	76		39	28	9
		48	18	21	9
Anorexia	60		30	24	6
		30	15	9	6
Fever	12		5	3	4
		6	3	3	—
Sweating	30		24	—	6
		32	29	—	3
			Gain	No change	Loss
Loss of weight	72		52	9	11
		45	30	9	6

The Results of Treatment with Intravenously Administered Tri-(2-chloroethyl)-amine Hydrochloride

Acute leukæmias.—No beneficial effects have been noted except in those few patients that presented first with raised leucocyte counts; in these cases a single dose of this therapeutic agent was often sufficient to lower the total leucocyte count, prior to specific treatment with aminopterin or cortisone (*see* Table I in Gardikas and Wilkinson, 1952).

Chronic leukæmias.—Some patients, especially elderly ones with only very slowly progressive or stationary chronic lymphatic leukæmias, may be so mild in symptoms and signs that no treatment is needed. These have been omitted from this list. In general I have considered as indications for treatment of chronic leukæmia a poor deteriorating condition, anæmia, rising leucocytosis, weakness, fatigue, loss of weight, sweating, marked splenomegaly and glandular enlargement.

The duration of remissions between courses has varied from less than a month to more than two years in some patients (Table II) while a very high proportion of the patients showed complete or considerable relief from the symptoms and signs of the condition (Table I). This has been particularly noticeable where there has been marked splenomegaly, hepatomegaly and glandular enlargement in any or many parts of the body, all glands being affected simultaneously by the injections of the tri-compound. The survival of these patients compares extremely well with the published results of corresponding groups treated by irradiation (Table III) in other centres.

TABLE II.—CHRONIC LEUKÆMIA: DURATION OF REMISSIONS BETWEEN COURSES OF NITROGEN MUSTARD

Months	No. of cases
> 24	2
13–24	11
7–12	14
4–6	31
1–3	59
< 1	9

TABLE III.—CHRONIC LEUKÆMIA: AVERAGE SURVIVAL SINCE START OF TREATMENT

Reference	No. of cases	Treatment	Average survival (months)
Myeloid leukæmia			
Hoffman and Craver (1931)	71	Irradiation	31
Vogt (1949)	86	Irradiation	19
Wintrobe and Hasenbush (1939)	23	Irradiation	20*
Wilkinson (1953) this series	69	Nitrogen mustard	29 (2–57)
Lymphatic leukæmia			
Vogt (1949)	65	Irradiation	19
Wilkinson (1953) this series	41	Nitrogen mustard	26 (1–34)

*Since diagnosis was established.

Hodgkin's disease (Table IV).—The dosage was controlled by the size of the glands, spleen or liver, and not by the relative insensitivity of the leucocytes to these therapeutic doses, in contradistinction to the hypersensitivity of the leucocytes in the chronic leukæmias. The effects of nitrogen mustard on Hodgkin's disease were most dramatic in most cases for the glands regressed rapidly so that in seven to fourteen days—sometimes less, according to dosage—in moderately severe cases they might be normal, or almost so. I have seen large masses of glands in neck, axilla, groin and mediastinum disappear in an incredibly short time without untoward incident, and I have also records of bone metastases clearing up with equal rapidity.

Recurrences frequently take place but again respond to further treatment. The only type that really fails is the young patient 15–30 years of age with a severe Pel-Ebstein syndrome, sweating profusely and continuously, but these patients do badly with any form of treatment.

7 patients with other reticuloses, 1 with lymphosarcoma, 6 with monocytic leukæmia showed only temporary partial remissions on adequate treatment (Table IV).

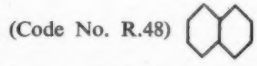
TABLE IV.—RETICULOSES

Tri-(2-chloroethyl)-amine hydrochloride

	No. of patients	Total dosage (mg.)	Regression of Splenomegaly	Regression of Enlarged lymph nodes	Survival (weeks)
Hodgkin's disease ..	54	6–174	Complete in 1 week – 6 2 „ –15 3 „ –17 4 „ – 3 Partial – 9 None – 4	Complete in 1 week – 6 2 „ –15 3 „ –19 4 „ – 5 Partial – 5 None – 4	16–404 (5 2 years) (18 1 year)
Reticuloses (miscell.)..	7	12–30	Temp. partial.	Temp. partial	2–17
Lymphosarcoma ..	1	108	Temp. partial	Temp. partial	56
Monocytic leukæmia..	6	12–30	None – 5 Partial – 1	None – 5 Partial – 1	1–12 Alive (52 weeks)
Myelomatosis.. ..	2	12–30	—	—	Treatment changed

β-NAPHTHYL-DI-(2-CHLOROETHYL)-AMINE (R.48)

The search for a satisfactory preparation that can be given orally led Professor Haddow and colleagues (1948) to produce a series of substances of which one,

β-naphthyl-di-(2-chloroethyl)-amine, (Code No. R.48)  $-N:(CH_2.CH_2.Cl)_2$

seemed worthy of trial, and he kindly made it available to us and others through the Medical Research Council (Gardikas and Wilkinson, 1951). It proved on the whole disappointing and distinctly inferior to the tri- and di- (2-chloroethyl)-amines given intravenously; it was found, however, to have some value in certain cases, especially of Hodgkin's disease, over long periods and for patients with poor veins. It is a milder, and less toxic substance.

The dosage employed was 50–800 mg. in divided doses daily orally, the more usual quantity being 100–300 mg. daily. Occasional toxic effects were noted such as hæmaturia, dysuria, purpura, and occasional nausea or diarrhœa, but these had no relationship to the amount or frequency of treatment.

The results of treatment were variable as will be seen from Table V but, in general, R.48 was of no value in any of the acute leukæmias, or lymphosarcoma. In chronic leukæmia (10 myeloid; 12 lymphatic) 3 of the 10 myeloid leukæmias showed good responses, living one and a half, two and three

TABLE V.—TREATMENT WITH β-NAPHTHYL-DI-(2-CHLOROETHYL)-AMINE (R.48)

	No. of cases	Daily dose (mg.)	Total amount given (grammes)	Regression of glands and spleen (days)	Response to treatment: Good	Fair	None	Toxic effects
Hodgkin's disease	19	50–300	2–45	50–150	5	8	6	Transient maculo-papular rash (1)
Chronic myeloid leukæmia ..	10	50–400	5–300	50–100	3	3	4	
Chronic lymphatic leukæmia	12	50–400	3·6–28	20–60	3	4	5	Hæmaturia (1) Dysuria (1) Purpura (1)
Acute myeloblastic leukæmia	2	400–800	6·8; 21·6	—	—	—	2	—
Acute lymphatic leukæmia ..	1	50	2·0	—	—	—	1	—
Mycosis fungoides	2	100–400	5–10	—	1	1	—	—
Lymphosarcoma	2	200–400	8–12	—	—	1	1	—

years respectively, and 3 fair responses to treatment, while 4 failed to benefit at all. Of the 12 lymphatic leukæmias, 3 gave good clinical responses, 2 being still alive after fifty-five and eight months respectively, while 4 showed fair improvement but 5 did not improve on R.48. 19 patients with Hodgkin's disease were treated; 5 showed good responses, and 8 fair improvement for a time on doses of 50–300 mg. daily, the spleen and glands showing marked or complete regression in size in fifty to one hundred and fifty days

Urethane

Urethane (ethyl carbamate, $NH_2.CO.OC_2H_5$) has been found to have marked depressant effects on the bone-marrow and especially on the leucopoietic elements in chronic leukæmias. It is given in doses of 1–3 grammes daily, the dose being reduced as soon as possible to the minimum as the leucocyte count falls; the spleen and lymph nodes may be reduced, but urethane has a very disconcerting way of suddenly producing aplastic anæmia, agranulocytosis or severe thrombocytopenic purpura after a variable interval of some weeks or months of apparently good control of the leukæmic process; proper control must be maintained by weekly determinations of the full blood count and platelets—leucopenia or thrombocytopenia may be the first sign of complete, irreversible marrow failure. Urethane has little value in the treatment of Hodgkin's disease, acute leukæmias, or other reticuloses, but I have produced relief of pain, temporary healing and regression of the bone changes and slowing of the disease process in 3 patients with multiple myelomatosis—1 is still alive after eighteen months of treatment having taken 697 grammes of urethane in that period (Table VI).

Table VI.—Urethane

Disease	No. of cases	Total dosage (grammes)	Survival (months)	Therapeutic effects
Hodgkin's disease	3	30–50	1–2	None
Chronic myeloid leukæmia ..	14	4–876	1–31	Temp. incomplete Aplastic anæmia Agranulocytosis Thrombocytopenia
Chronic lymphatic leukæmia ..	5	2–430	1–14	
Monocytic leukæmia	4	36–214	1–6	None
Acute myeloid leukæmia ..	6	1–126	3(days)–8	
Acute lymphatic leukæmia ..	3	3–48	1(day)–3	
Myelomatosis	4	4–[697]	2(days)–[18]	Relief pain. Temp. healing. Slowing of disease (3)
Other reticuloses	5	20–100	1–2	None

Aminopterin

I have dealt very fully with the folic acid antagonists, in particular aminopterin, in a lecture in 1947 to the Section of Experimental Medicine (Wilkinson, 1948; Wilkinson and Gardikas, 1951) and need only refer to the report on the beneficial effects of the folic acid antagonists in children with acute leukæmia (Farber, 1949; Farber *et al.*, 1948). Since then varying experiences have been described by other workers with generally disappointing results. In our hands aminopterin did not prove to be of any value in the treatment of the chronic leukæmias, Hodgkin's disease and other reticuloses. Of patients with acute leukæmia, 28 acute myeloblastic, lymphatic and monocytic leukæmias failed to respond to its influence, but 8 showed partial remissions (twenty to sixty days), and 2 complete remissions for up to sixty-two days (Table VII). The dosage employed was 1 mg. orally or subcutaneously daily or on alternate days until toxic manifestations or severe leucopenia developed. The chief toxic features were stomatitis, diarrhœa, hæmorrhagic rashes, epistaxes, alopecia, and leucopenia with thrombocytopenia, but it is difficult to be certain whether some of these were not part of the acute leukæmia itself (Wilkinson and Gardikas, 1951). While disappointing in their ultimate effects, nevertheless in co-operation with other agents (e.g. ACTH, and cortisone) better results have been obtained.

Cortisone and ACTH

Many varied opinions have been expressed as to the value of these hormones in the treatment of leukæmias, reticuloses, and allied conditions. In general our experience has been disappointing in view of the perhaps extravagant claims that have been made by others. The experience of the Hæmatology Panel of the Medical Research Council (1952) did not lead to the feeling that these hormones were of much value in the treatment of disorders of the blood, and of the reticuloses; only some of the acute leukæmias in children seemed to show temporary partial remission.

In my group of patients we found that there were no beneficial effects following the administration of these hormones in chronic leukæmias, Hodgkin's disease, myelomatosis, and other reticuloses (Table VIII). Of the acute leukæmias, 28 patients failed to show any improvement (Table IX). On

TABLE VII.—ACUTE LEUKÆMIA: PARTIAL OR COMPLETE REMISSION FOLLOWING AMINOPTERIN

Case No.	Sex	Age	Type of leukæmia	Total dose (mg.)	Length of remission (days)	Duration of leukæmia since treatment began (days)
				Partial Remission		
1	M	6	Myeloblastic	17	20	75
2	M	13¾	,,	Met-Fol.B 100 + aminopterin 6	60	120
3	M	4	,,	3	20	60
4	F	5	,,	(*a*) 5 (*b*) 10	(*a*) 42 (*b*) —	113
5	F	4¼	Lymphatic	3	30	77
6	F	2¾	,,	(*a*) 5 (*b*) 3	(*a*) 60 (*b*) —	172
7	M	5½	Monocytic	14	60	264
8	F	7	,,	5	34	72
				Complete Remission		
9	M	15	Myeloblastic	15	30	63
10	F	2¼	Lymphatic	(*a*) 9 (*b*) 5	(*a*) 62 (*b*) 60	187

TABLE VIII.—RETICULOSES: ACTH OR CORTISONE

Case	No.	Total dosage	Therapeutic effects	Duration of life (weeks)
Hodgkin's disease	6	ACTH 500–2,000 Cortisone 700–2,000	None	—
Follicular lymphoblastoma ..	2	ACTH 1,400–2,805 Cortisone 1,000–1,600	Poor or none	1–32
Myeloid reticulosis	4			
Acute reticulosis	3			
Reticulum cell reticuloses ..	1		Slight temp. improvement	14
Chronic leukæmia	5	Cortisone 750–2,000	None	—
Acute leukæmias (rare types)	6	ACTH 500–1,500 i.m. ACTH 100 i.v. Cortisone 1,000	None	1½–10
Mycosis fungoides	3	Cortisone 1,000–2,000	Partial	—
Myelomatosis	3	ACTH 1,400–2,000	None	3–4

TABLE IX.—ACUTE LEUKÆMIA: NO RESPONSE TO CORTISONE OR ACTH

	Cases			Age		Total dosage (mg.)	Start of treatment to death (days)
	Male	Female	Total	Male	Female		
Acute myeloblastic leukæmia ..	8	5	13	4–40	5–47	A/120–2,400 C/250–1,300	5–150
Acute lymphatic leukæmia ..	8	2	10	3–62	8–61	A/200–2,500 C/100–1,600	6–21
Acute monocytic leukæmia ..	4	1	5	10–64	65	A/300–850 C/720–2,000	5–40

A=ACTH
C=Cortisone

the other hand, 16 patients have shown partial or complete remissions temporarily, but relapsed later (Table X); in general, the child with acute lymphatic leukæmia and no gross splenomegaly does the best. 3 of these patients showed full and complete remissions and are alive and well at the present time of writing—1 being completely normal clinically and hæmatologically in every way, and has been without any treatment for over twelve months.

TABLE X.—ACUTE LEUKÆMIAS RESPONDING TO CORTISONE OR ACTH

Case	Total dosage mg.	Response to treatment	Splenomegaly lymph nodes	Duration of life from treatment to death (weeks)
Acute Myeloblastic Leukæmia				
M 7	C. 1,000	Partial		10
M 5	(1) A. 900 (2) C. 1,100	P nil	Regressed completely	15
F 56	C. 5,000	P	or considerably until	14
F 6	C. 1,000	P	relapse	17
M 3	(1) A. 480 (2) C. 900	P nil		31
M 16	(1) C. 3,000 (2) C. 3,200	Full	Complete regression with normal blood and marrow	Alive and normal (10 weeks) no treatment
Acute Lymphatic Leukæmia				
M 6	A. 800	Partial		8
F 5	(1) A. 650 (2) A. 200 (3) C. 900	P		18
F 4	(1) A. 480 (2) C. 275	P	Regressed completely or considerably until	9
F 2½	C. 2,775	P	relapse	16
F 2¾	C. 1,200	P		14
M 5	C. 750	P		14
M 5	C. 2,700	P		Alive (13 weeks)
F 2½	C. 2,000	P		Alive (8 weeks)
F 5	C. 9,500	Full	Complete regression with normal blood and marrow	Alive and normal (76 weeks) no treatment
M 19	(1) A. 1,850 (2) C. 350	Full		33

1:4—DIMETHANESULPHONYLOXYBUTANE (G.T.41; C.B.2041; MYLERAN)

Myleran ($CH_3.SO_2.O.CH_2.CH_2.CH_2.CH_2.O.SO_2.CH_3$) is a substance that was kindly supplied to me for trial by Professor Haddow and his colleagues (Haddow and Timmis, 1953; Galton, 1953). As they had found, so we confirmed that it was only of value in the treatment of chronic myeloid leukæmia which can be fairly well controlled so far as our present knowledge goes. The dosage requires great care in adjustment—depending on the degree of leucocytosis; as originally suggested we gave an initial dose of 25 mg. orally for three to five days, and after the full effects had been developed in the course of two to three weeks a maintenance dosage of 2–4 mg. daily or on alternate days was given according to the then leucocyte count. Great care is needed in increasing or continuing the doses owing to the profound effects of this substance on all the elements of the marrow, producing in excess dosage aplastic anæmia, thrombocytopenic purpura and agranulocytosis. This is particularly liable to occur in chronic lymphatic leukæmia and other reticuloses for which it is of no value.

Most chronic myeloid leukæmias showed response to this treatment in the beginning, the spleen diminishing in size as the leucocyte count fell, but some patients failed to maintain improvement, developing anæmia or marrow aplasia, or just failing to keep the leukæmic process under control.

In our series 18 patients (6 males, 12 females) responded well in the beginning, and after intervals of five to fifteen months there had been good clinical responses in 15; 6 patients had leucocyte counts less than 10,000, and 13 had less than 30,000 leucocytes. Of these, 5 failed to maintain the improvement and relapsed with anæmia (after five and six months respectively), aplastic anæmia (eight months), hypoplastic anæmia (eight and a half months) or increased leucocytosis often with further enlargement of the spleen once again: 1 patient developed thrombocytopenia (ten months) but after discontinuance of treatment and several blood transfusions recovered, and is now well after fifteen months. 13 patients are still well and under control on doses of 2–4 mg. daily or alternate days. Splenomegaly diminished considerably in 12, slightly in 4, and not at all in 2.

TRIETHYLENE MELAMINE (T.E.M.)

This substance, which Dr. Nabarro is to discuss, is in our experience the most toxic of all the chemotherapeutic agents as yet tried—producing thrombocytopenia, aplastic anæmia, neutropenia or agranulocytosis in a large proportion of the cases receiving it in even quite small doses of 1–10 mg. orally or intravenously. Under no circumstances should it be made available for general use or ever employed without the most strict hæmatological control. In our experience its effects were variable in chronic leukæmias and Hodgkin's disease, but at least 50% of patients will show neutropenia, agranulocytosis or aplastic anæmia.

Summary

The main features and effects of these chemotherapeutic agents are summarized in Table XI from which it will be seen that intravenous tri-(2-chloroethyl)-amine hydrochloride is very effective and can be easily controlled in the treatment of chronic leukæmias and most reticuloses; Myleran is of great value for chronic myeloid leukæmia, while urethane is also effective in some chronic leukæmias at least for a time. Aminopterin, ACTH and cortisone have been of value in some acute leukæmias, but of no value in other reticuloses and chronic leukæmias; triethylene melamine is too dangerous and toxic for safe use in these conditions.

TABLE XI.—CHEMOTHERAPEUTIC AGENTS

Agent	Effective dose	Toxicity	Therapeutic value	Toxic effects
Tri-(2-chloroethyl)-amine (Lekamin) Di-(2-chloroethyl)-methyl-amine	4–6 mg. i.v. as required	Slight in therapeutic doses	Chronic myeloid, and lymphatic leukæmia, Hodgkin's disease, some reticuloses	Some nausea, vomiting
β-Naphthyl-di-(2-chloroethyl)-amine (R.48)	100–800 mg. orally daily	Slight	Hodgkin's disease chronic leukæmia	Nausea, purpura, hæmatemesis, dysuria, diarrhœa
Urethane	0·5–3 grammes orally daily	Moderate variable	Chronic leukæmia	Aplastic anæmia, thrombocytopenic purpura, agranulocytosis
1:4-dimethanesulphonyloxy-butane (G.T.41; Myleran)	100–125 mg. orally	Marked	Chronic myeloid leukæmia	Aplastic anæmia, thrombocytopenic purpura, agranulocytosis
Triethylene melamine (T.E.M.)	1–10 mg. orally daily	Very marked	Variable—chronic leukæmia	Nausea, vomiting, diarrhœa, aplastic anæmia, agranulocytosis, thrombocytopenic purpura
Aminopterin	Up to 1·0 mg. orally or i.m. daily	Marked	Fair; variable in acute leukæmia	Thrombocytopenia, loss of hair, ulceration of mouth
Cortisone, ACTH	Up to 300 mg. daily	Slight	Fair; variable in acute leukæmia	Various

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Professor A. Haddow: The various chemical agents used in the treatment of the reticuloses induce their effects by very different means, (1) whether endocrine, as in the action of cortisone and ACTH in acute leukæmia, (2) through antagonism of a specific nutrilite, as in the case of the so-called folic acid antagonists also in acute leukæmia, (3) through an effect upon maturation, or differentiation, as for urethane in chronic myelogenous leukæmia and myelomatosis, and (4) by a more direct cytotoxic or cytostatic mechanism exemplified by the nitrogen mustards, both aliphatic and aromatic, and by other chemical types, more recently discovered and acting by the same or a similar direct mechanism, such as the polyethyleneimines and a new series devised by G. M. Timmis of which Myleran is a member, active in chronic myelogenous leukæmia. Members of the last type are believed to produce their effects through chemical alkylation of protein or nucleoprotein in the cell, and hence have come

to be known as "biological alkylating agents". This property is preponderantly directed against cells in an active state of division, whether malignant or not. Hence, in applying such agents we interfere not only with the division of the tumour cell but with that of many normal cells as well, especially in the bone-marrow and the reproductive organs. This recalls the opinion of J. A. Murray, the distinguished Director of the Imperial Cancer Research Fund, twenty years ago, when he doubted the possibility of our ever being able to suppress the growth of the cancer cell, without producing equivalent damage to normal cells at the same time. This lack of specificity still remains the most powerful limiting factor. The second lies in the fact that the tumour cells themselves, in all too many cases, soon become refractory to the inhibitory effect of the chemical agent, presumably through the selection of resistant forms, by the induction of drug-resistance, or by a combination of both. What I have to say will illustrate both these difficulties only too clearly. At the same time it should be realized that the chemotherapy of the reticuloses, as of cancer generally, is still in its veriest infancy.

Anything I have to say of clinical observations made at the Royal Cancer Hospital is entirely due to the work of my clinical colleagues there, and especially that of D. A. G. Galton.

Cortisone and ACTH in Leukæmia and Allied Diseases

Many workers, including Pearson, Farber, and Wintrobe, have reported on the use of ACTH and cortisone in acute leukæmia in both adults and children. On a dose of 25 mg. six-hourly in adults, and about half this dose in children, approximately 50% of cases may enter complete clinical and hæmatological remission. In these, chemical studies often indicate a mass destruction of leukæmic tissue. Great variation is observed from patient to patient in regard to the cytological, physiological and biochemical effects of the hormones. The remaining cases do not respond, even to much increased dosage, and those undergoing remission inevitably relapse either during treatment or after it, the great majority proving unresponsive to subsequent therapy. Pearson and his colleagues have also studied the effect of ACTH on the chronic lymphomas, including chronic lymphatic leukæmia, lymphosarcoma, Hodgkin's disease, and related conditions. During the period of investigation there was rapid regression of the lesions, but the underlying pathological conditions were not significantly changed, and the lesions rapidly returned when administration of ACTH was discontinued. In the opinion of Mickle, ACTH and cortisone are of less value than aminopterin in the treatment of acute leukæmia in children. Dameshek commenting on the recent report by the Hæmatology Panel of the Medical Research Council, says that in the acute and subacute leukæmias of infancy and childhood, the steroid hormones induce a well-defined and even a complete remission in about 50–60% of the cases. If ACTH or cortisone is given simultaneously with aminopterin a remission may be induced in almost every case. Although in most cases the remissions are not sustained for more than two to four months, in some cases excellent and even complete clinical and hæmatological remissions continue for a year or longer. ACTH and cortisone may also, not infrequently, be useful in chronic lymphocytic leukæmia. The difference of opinion is attributed largely to the dosage used: the cases referred to in the Medical Research Council report received 1 gramme ACTH and 1·5 gramme cortisone over ten days, whereas in Dameshek's opinion ACTH must be given in amounts of from 150–300 mg. daily, and even this is sometimes ineffective.

Antagonists of Folic Acid and of the "Citrovorum" Factor, in the Treatment of Acute Leukæmia

As for many other agents in cancer chemotherapy, interest in the so-called folic acid antagonists is divided between the fundamental problem of their mode of action and of their practical application. On the fundamental side Sauberlich in 1949 discovered that the *Leuconostoc citrovorum* factor is capable of reversing the effects of aminopterin, and the factor was identified and synthesized by Brockman and others in the following year. The reversal of aminopterin toxicity by the citrovorum factor has also been studied by Schoenbach, Cravens and Snell, Greenspan, Earle, and others, with support to the hypothesis that aminopterin interferes with the enzymatic conversion of folic acid to the citrovorum factor, as well as with the enzymes involved in the further metabolism of the citrovorum factor itself. Both folic acid and the citrovorum factor have close interrelations with the metabolism of purines, pyrimidines, nucleosides, nucleotides and nucleic acids; and from the work of Skipper and others it appears that the folic acid antagonists may conceivably operate through an inhibition of nucleotide synthesis.

From a great number of papers on the practical application of these agents, the results of therapy with aminopterin and its analogues such as amethopterin and aminoanfol appear to fall into three classes, namely, no response, temporary clinical improvement, and, in the smallest number, remarkable and complete remissions which usually last for a short period only, but which may on occasion be prolonged. Thus the most favourable results so far achieved in the treatment of acute lymphatic leukæmia in childhood have been obtained with aminopterin and related compounds, in the shape of remissions lasting over a year. Even though administration of these drugs is as a rule limited by the early development of toxic effects, it is remarkable that remission can be induced at all in such conditions, hence the fundamental importance of the observations themselves.

Urethane in Multiple Myeloma

Although urethane is capable of producing useful responses in chronic myeloid leukæmia, in which according to Whitby it may be as effective as, and less misery-making than, X-rays, it has almost certainly been superseded by Myleran. Longer remissions may be achieved by Myleran and these are not infrequently maintained for considerable periods even when the drug is withdrawn. The employment of urethane in multiple myeloma has been studied by Rundles, who describes how, as plasma-cell growth is inhibited by urethane, abnormal serum components are reduced or may virtually disappear. Rundles and his co-workers also mention an observation made in a case in which benefit from ten months' continuous urethane therapy was followed by relapse. When urethane was discontinued, the plasma cells in the marrow again decreased and proteinuria diminished, a phenomenon which these authors interpret as indicating that the prolonged exposure to urethane had rendered the plasma cells nutritionally dependent, so that their growth was once again inhibited by the drug's withdrawal.

Harrington and Moloney also report a number of cases of multiple myeloma treated with urethane, of which a proportion showed relief of pain, gain in weight, improvement in anæmia, reduction in abnormal serum proteins, suppression of plasma-cell proliferation and probable prolongation of life. A further series of 66 proved cases treated with urethane over a two-and-a-half-year period is provided by Luttgens and Bayrd. Again there is some over-all suggestion of prolongation of life. However, only 50% showed subjective improvement, and 20% objective improvement. While their results appear not as favourable as in other series, these authors believe the administration of urethane to be probably as good treatment as is available for multiple myeloma at the present time.

While urethane has doubtless been useful in a limited sense, again its main interest probably lies in its mechanism of action: this is still obscure, although much has been contributed by Skipper and his school employing labelled compounds—especially the suggestion that urethane may inhibit the incorporation of formate in nucleic acid synthesis.

The Nitrogen Mustards in the Therapy of Hodgkin's Disease, the Leukæmias and Reticuloses

Recognition that the nitrogen analogues of mustard gas, or the so-called nitrogen mustards, can induce cytotoxic effects in a wide variety of tissues, and especially those in a state of active proliferation, originated from the study of these substances as potential agents of chemical warfare. A remarkable feature of the mustards is the way in which they reproduce many of the biological effects of high energy radiations. Useful clinical responses are very largely confined to the spectrum of neoplastic disease involving the reticulo-endothelial system—the leukæmias, multiple myeloma, lymphosarcoma and reticulum-cell sarcoma, Hodgkin's disease, giant follicular lymphoblastoma, polycythæmia vera, mycosis fungoides, Boeck's sarcoid, and other but rarer allied conditions. The nature and extent of the response is preponderantly determined by the histogenesis of the tumour and by the inherent activity of the given compound, and cannot appreciably be improved by mere modification in technique of administration.

In the treatment of Hodgkin's disease, most workers express the opinion that nitrogen mustard therapy should not be regarded as an adequate substitute for irradiation, but should be reserved for cases with marked constitutional symptoms and visceral involvement. In these, a period of marked rehabilitation may follow the use of one or several courses, although opinion is doubtful whether, in fact, the advent of the nitrogen mustards has seriously, if at all, modified the basic prognosis. They may, however, be used with profit in cases for which radiotherapy is no longer suitable, and, in a proportion of those, surprisingly good responses may be obtained. They may also prove a valuable substitute for X-ray therapy in mycosis fungoides, and encouraging results, with prompt hæmatological and clinical responses, are frequently although not invariably observed in polycythæmia vera.

The nitrogen mustard most commonly employed is methyl-bis(β-chloroethyl)-amine or HN_2: the corresponding tri- compound HN_3 is more toxic but has been successfully used by Dr. Wilkinson in the treatment of the chronic leukæmias. Much labour and ingenuity have been spent in an endeavour to produce variants of enhanced therapeutic efficiency—at the Royal Cancer Hospital especially by the late Professor Kon, W. C. J. Ross, and others—and several aromatic derivatives are now available which have one advantage in that they can be administered for long periods orally, and produce no acute side effects. One of these, β-naphthyl-di(2-chloroethyl)-amine, has been extensively studied in clinical trial at the Royal Cancer Hospital and elsewhere, but with relatively disappointing results which indicate that it is less active than HN_2, slower in action, and produces remissions which are less in frequency and extent, and are of shorter duration, than those produced by the aliphatic nitrogen mustards. It may, however, be helpful in the treatment of polycythæmia vera.

Triethylene Melamine

Apart from their clinical application, much attention has been paid in the past few years to the more fundamental aspects of the action of the nitrogen mustards. On the basis of a correlation between biological activity and the presence in the molecule of a minimum of two reactive side-chains, Goldacre,

Loveless and Ross suggested that the biological effects of these substances might primarily be due to a process of chemical cross-linkage between the constituent molecular chains of the chromosome fibre. While this view is now known to be unduly simple, and other possibilities are equally likely, it has led to the general conception of the action of these and similar agents by virtue of the alkylation of genetic protein. In this way the hypothesis has provided a remarkable stimulus to the development of the subject and to the search for alkylating agents of increased therapeutic efficiency—for example, among various substances already utilized as cross-linking agents in the textile industry, among which many di-epoxides and polyethyleneimines have now been shown to possess cytotoxic activity of the same general type as that already known in the case of the mustards.

The triethylene melamine known as T.E.M. (2:4:6-triethyleneimino-*s*-triazine), is of special interest since it was originally devised by the Hoechst Farbwerke as a cross-linking agent of high efficiency, and was later described by Lewis and Crossley, and by Burchenal and others, as capable of retarding the growth of various mouse leukæmias and other tumours. The toxicity of this substance is about twice that of HN_2, and therapeutic responses are obtained in the range of from 8 to 12 mg. total dosage in the adult. Since it can be given intravenously without venous thrombosis or severe nausea or vomiting, and is therapeutically as active as HN_2, it has tended of late to supplant the latter in clinical practice. Rhoads and his colleagues have described how oral administration will induce temporary objective and subjective improvement in Hodgkin's disease and in chronic myelogenous and lymphatic leukæmia. Indications are similar to those for HN_2, and the slower and more prolonged action by oral administration may make it more useful. In 43 cases, Bayrd found results to be most favourable in chronic myelogenous leukæmia, less so in chronic lymphatic leukæmia, Hodgkin's disease and lymphosarcoma. Meyer studied 17 cases of chronic leukæmia treated in total doses of 10–125 mg. over periods of 10–200 days, in courses ranging from 10–20 mg. Complete hæmatological remissions occurred in 2 cases of chronic lymphatic leukæmia, but otherwise results were distinctly variable. Although in the hands of Paterson and Boland T.E.M. appeared equal to established methods of treatment in cases of leukæmia, polycythæmia, Hodgkin's disease, and myelomatosis, these authors did not regard it as in any way superior. Treatment must be extremely closely controlled to avoid serious depression of the marrow. Thus Shimkin points out the disadvantage of T.E.M.'s narrower chemotherapeutic range of dose, as compared with HN_2, and mentions that the oral dose in lymphatic leukæmia, which may be extremely sensitive, should not exceed 0·1 mg./kg. body weight. According to Hansen and Bichel, depression of the bone-marrow occurs later than with nitrogen mustard, lasts longer, and may sometimes be irreversible.

Our own experience over the past two and a half years has been limited to 20 cases of Hodgkin's disease and 14 of lymphosarcoma. Of the 20 cases of Hodgkin's disease, the majority were young adults, most had received X-radiation earlier, and all were in an advanced or generalized state of the disease, with toxic symptoms prominent. 8 were treated by the intravenous route and 12 by the oral. The maximum intravenous dose at one injection was 2 mg., and the maximum total i.v. dose 12 mg. The maximum single dose orally was 10 mg. and the average 5 mg., while the maximum total oral dose, and the maximum tolerated, was 50 mg. This is now known to be excessively high, since in one case agranulocytosis followed a total of 35 mg. in 5 mg. doses. Of the 20 cases, 12 obtained remissions lasting two to six months, of real value in most. Of these, 4 received 1 or more subsequent courses which were never as effective as the first. In 2, both of whom had also received further X-ray treatment, fatal aplasia of the marrow supervened. In general, the more satisfactory remissions appeared as good as those from HN_2, but subsequent courses appeared not only less effective but dangerous, seeming to render the patient liable to much greater marrow damage from subsequent X-rays.

Of the 14 cases of lymphosarcoma, 11 were treated by the oral route and 3 intravenously. The maximum intravenous dose at one injection was 2 mg., the maximum single oral dose 15 mg., and the maximum total oral dose 75 mg. Again this is much too high, since agranulocytosis followed administration of 20 mg. in four days in one case, and of 25 mg. in five days in another. Of the 14 cases only 2 showed useful regressions, the drug either producing no effect in the remainder, or regression accompanied by severe depression of the marrow.

In sum, and even allowing the advanced stage of the disease in most of these cases when treatment was started, our experience with T.E.M. has, in general, been depressing.

Myleran in the Treatment of Chronic Myelogenous Leukæmia

Following the detection of high tumour-inhibitory activity in various sulphonic acid esters synthesized by Timmis, it was decided that the correlation between chemical constitution and activity could best be studied by utilizing a simple structure to carry the functional groups, and one which would be easily capable of modification in regular gradations.

A series of dimethanesulphonyloxyalkanes was therefore synthesized, in which the number of carbon atoms in the central chain varied from 2 to 10. Biological activity is at a peak where $n = 4$ or 5. In the former case (1:4-dimethanesulphonyloxybutane), the compound has a specially

pronounced action on the granulocytes, which observation has led to its clinical trial by Galton in cases of chronic myelogenous leukæmia, to which its use would so far appear to be confined.

In a series of 19 patients to whom the substance was given orally, relief of symptoms, general improvement, regression of enlarged spleen, rise in hæmoglobin level, and fall in the leucocyte count with improvement in the differential count, have all been observed. While all cases responded initially, 9 relapsed within six months. However, 8 patients obtained remissions of 23 months, 18, 18, 15, 14, 13, 10 and 6 months respectively. The response in 3 patients who had received no previous treatment was comparable with the best results of radiotherapy. 5 of 9 patients for whom radiotherapy was not advised obtained useful remissions, and the remaining 4 outstandingly successful remissions. In 3 cases the response to Myleran compared unfavourably with what might have been expected of radiotherapy, but excessive dosage may have been responsible by causing irreversible damage to the marrow in 1 case and by leading to drug resistance in the other 2. Thrombocytopenia is the only important side effect, but is unlikely to be serious if large doses are avoided and if treatment is withheld when the platelet count is below 100,000.

The drug is more selective than the nitrogen mustards or the folic acid antagonists in its effect on myeloid cells, and may be somewhat safer in use: many cases have received daily doses by mouth of 4 mg. for several months. In such doses, although it depresses myelopoiesis, it has little effect upon the lymphocytes and platelets, and side effects are absent. Larger doses, however, depress the platelet count and cause hæmorrhagic symptoms, and there is a danger of causing an irreversible depression of the marrow which may not become obvious for four to six months. These effects show the necessity for the strictest hæmatological control. Dr. Galton has carried out a most careful comparison of the responses to high and low dosage and as a result makes a plea, which I endorse, for the avoidance of higher doses. The drug is of no value in the acute leukæmias, or in acute relapse of the chronic leukæmias. Nevertheless it is of interest, within its severely limited application and in the most favourable cases, as having yielded substantially useful clinical results equal to or surpassing those provided by chemical agents in this or other forms of malignant disease.

According to Galton, if a new remedy is to compete successfully with radiotherapy it must be as efficacious and must be safe, free from undesirable side-effects, and easy to administer. An essential feature of radiotherapy is that it can induce remissions repeatedly, and in considering the claims of Myleran to a place in therapeutics he emphasized that little is yet known of its action on relapse following prolonged first remission. From what is beginning to be known, however, it appears the situation should be treated with considerable reserve, certain of such second responses having so far been less satisfactory, with in some cases minimal splenic regression, depression of platelets, and even acute relapse.

In the chemotherapeutic control of the reticuloses it seems to me improbable that any of the agents I have mentioned will find a permanent place. At the same time I should regard nothing more certain than that all these diseases will in time come under the influence of chemical agents immeasurably more powerful and specific than any we have at our command to-day. Firstly, there are indications from the most recent work that we have by no means sufficiently exploited the improvements to be expected on the basis of what is already known. Secondly, the more fundamental study of these various agents will almost certainly lead to advances of an altogether different kind, and thus render obsolete our present resources and ideas.

Dr. J. D. N. Nabarro: Nitrogen mustard has been shown to influence the course of Hodgkin's disease and other malignant lymphomata, and the indications for its use as a palliative agent in preference to deep X-rays are fairly well defined (Nabarro, 1949). If the lymphomatous process is well localized, deep X-ray therapy gives more complete and more prolonged remissions. In cases in which there is evidence of generalized disease, especially if associated with constitutional disturbances, for example fever and anorexia, chemotherapy should be considered. There are three difficulties in the use of nitrogen mustard. It has to be given intravenously, and unless the injection is made into the tubing of a fast running saline drip there is a high incidence of thrombosis. Secondly, about 70% of patients given the "bis" derivative, di-(2-chloroethyl)-methylamine hydrochloride—Mustine, get severe vomiting, and this is most distressing in patients already seriously ill. Thirdly, bone-marrow depression and fatal aplastic anæmia may follow its use.

After the introduction of nitrogen mustard, intensive studies were undertaken in many centres to find new derivatives that were equally effective and less liable to produce complications. One drug merits further trial, 2:4:6-triethylenimino-*s*-triazine, also known as triethylene melamine or T.E.M. This agent was discovered independently in this country (Rose *et al.*, 1950) and in the United States (Burchenal *et al.*, 1950). Early studies showed that it was therapeutically active and that it had certain advantages when compared to nitrogen mustard (Karnofsky *et al.*, 1951; Paterson and Boland, 1951). It can be given intravenously by direct injection without fear of venous thrombosis and furthermore is effective by mouth. It is much less likely to cause vomiting and this is never so severe as after nitrogen mustard. On the other hand bone-marrow depression and pancytopenia are readily induced.

Results

We started using T.E.M. at University College Hospital in August 1951 and we have records of 22 patients treated with the intravenous preparation and 26 by oral administration. Most of our cases were of Hodgkin's disease or other malignant lymphomata, many had had previous deep X-ray therapy, but were now considered on account of dissemination or constitutional disturbance more suitable for a trial of chemotherapy. A few had had no previous treatment but were thought after consultation with Dr. E. L. G. Hilton, the physician in charge of the Radiotherapy Department at the hospital, to be more likely to benefit from drug treatment. Many of the patients were referred by Dr. Hilton and her colleagues to whom my thanks are due.

The results of 29 courses given intravenously to 22 patients are shown in Table I, together with the criteria used for assessing the results; this is important because many reports have been over-enthusiastic in their evaluation of chemotherapeutic agents for malignant disease. The assessment is based on the patient's capacity for activity and work, and on the relief of distressing symptoms, but all patients who derived moderate or considerable benefit from the treatment also showed objective evidence of improvement. The results given in this Table are disappointing, but the dose used was rather small, and in this initial trial many advanced, often terminal cases were included. The 2 patients shown as obtaining considerable benefit had excellent remissions of nine months' duration.

TABLE I.—INTRAVENOUS T.E.M. THERAPY

Results obtained in 22 patients given 29 courses of 0·08–0·2 mg./kilo body weight—mean 0·14 mg./kilo

Disease	Number of patients	Considerable benefit	Moderate benefit	Transient symptomatic relief	Failure
Hodgkin's disease	9	1	0	3	5
Stem-cell lymphoma	1	0	0	0	1
Lymphoblastic lymphoma ..	2	0	0	0	2
Lymphocytic lymphoma ..	1	1	0	0	0
Clasmatocytic lymphoma ..	4	0	0	1	3
Unclassified lymphoma ..	2	0	0	0	2
Chronic myeloid leukæmia ..	1	0	0	1	0
Carcinoma of bronchus	2	0	0	1	1

Criteria of Assessment

Considerable benefit—able to return to their normal occupation for at least three months.
Moderate benefit—able to leave hospital and be about the home for at least three months.
Transient symptomatic relief—control of distressing symptoms or any remission lasting less than three months.

The results in 26 patients given oral T.E.M. which are shown in Table II are more encouraging, but in some cases treatment failed to influence the progress of the disease. A satisfactory response cannot be related to any clinical or histological picture, and it is impossible, without trial, to forecast what effect treatment will have in any particular patient. The 8 cases of Hodgkin's disease, shown as deriving considerable benefit, have been controlled by repeated courses for from three to six months,

TABLE II.—ORAL T.E.M. THERAPY

Results of treatment in 26 patients

Disease	Number of patients	Considerable benefit	Moderate benefit	Transient symptomatic relief	Failure	Too recent to assess
Hodgkin's disease	17	8	1	2	3	3
Clasmatocytic lymphoma ..	1	0	0	1	0	0
Lymphoblastic lymphoma	3	1*	0	0	1	1
Lymphocytic lymphoma ..	1	0	0	0	0	1
Unclassified lymphoma ..	3	0	0	0	3	0
Carcinoma of bronchus ..	1	0	0	0	1	0

*Combined therapy of T.E.M. and cortisone, in a patient with a hæmolytic anæmia associated with lymphoblastic lymphoma.

and 5 are still responding well to the treatment. The length of remission following a single course has been from three to five months, but in 2 patients each given four courses of treatment it was noticeable that the remissions became progressively shorter and the hæmatological side effects more pronounced. [Slides were shown illustrating the effect of T.E.M. therapy on the fever, anæmia, splenomegaly and mediastinal lymphadenopathy of patients with Hodgkin's disease.]

Complications of T.E.M. Therapy

Intravenous therapy did not lead to venous thrombosis, and nausea and vomiting were minimal. The complications of oral therapy are shown in Table III. Nausea was common in patients given

Table III.—Complications of Oral T.E.M. Therapy

26 patients—49 courses—167 doses

Nausea: after 53% of doses
The incidence varied with the amount given—after 5 mg. 70%: after 3 mg. 28%.

Vomiting: after 4·7% of doses
Only occurred after doses of 5 mg. (Incidence 7·5%).

Possible *impairment of renal function:* 2 patients.

Hæmatological Complications:
After the initial course: Transient leucopenia: 1 patient.
Transient thrombocytopenia with purpura: 1 patient.
After prolonged treatment: Transient pancytopenia: 1 patient.
Persistent pancytopenia: 4 patients.

Leucopenia—W.B.C. $<1{,}000$ per c.mm.
Thrombocytopenia—Platelets $< 50{,}000$ per c.mm.
Pancytopenia—W.B.C. $< 1{,}000$: platelets $< 50{,}000$: reticulocytes $< 0{\cdot}1\%$.

the larger doses and continued for some days after the course was completed, vomiting was exceptional and never severe. Hæmatological complications were common, and persistent pancytopenia developed in 4 patients who received repeated courses of the drug.

Management of T.E.M. Therapy

Oral T.E.M. is an effective and easily administered form of palliative therapy for selected cases of malignant lymphoma. At the same time prolonged treatment has proved dangerous and unless a reasonably safe scheme of dosage can be evolved, the drug is unlikely to gain general acceptance. Three programmes have been suggested. One, which may be called "continuous therapy", consists of giving small doses at weekly intervals, each dose being preceded by a blood count. Remissions may be obtained in this way, but only after four or five weeks, and evidence of severe bone-marrow depression may suddenly appear after several months' treatment. We tried this method in a few cases, but gave it up after studying the American reports. The second programme may be called "intermittent therapy"; a short intensive course is given and only repeated when there is evidence of re-activation of the disease. A modification of this method involves re-treatment before there is re-activation—the so-called maintenance therapy. In most of our cases we have adopted the intermittent dosage programme without maintenance therapy.

The two important questions that have to be considered are the amount of T.E.M. that should be given in the initial course, and how soon treatment can safely be repeated. Dose should be based on the patient's body weight, and it seems from the results in our more successful cases that 0·25 mg./kg. body weight is usually an adequate therapeutic dose. On the other hand the bone-marrow of different individuals and in different diseases varies greatly in sensitivity. We have not had any persistent damage after the initial course, but it has been reported by others, and it is probably safer to give only 0·2 mg./kg. body weight in the first course. We use enteric-coated tablets[1] which give more consistent absorption (Paterson *et al.*, 1953). The course is given in divided doses on consecutive days and no single dose has exceeded 5 mg. If after ten days the white cell count has not fallen appreciably the course was not the maximum the patient could tolerate and a further 0·07 mg./kg. should be given. When there is anything to suggest bone-marrow involvement, a leukæmic blood picture for example, the initial course should be considerably smaller.

The ease with which serious bone-marrow depression can be produced is the over-riding consideration in the planning of subsequent treatment. Persistent pancytopenia developed in 4 of our patients

[1] Supplies of T.E.M. used in this trial were provided by Imperial Chemical (Pharmaceuticals) Ltd.

and it is perhaps of value to examine their progress to see if any conclusions can be drawn about how to avoid this complication (Fig. 1). In the first 2 patients, although an appreciable fall in the white cell count followed the first course of treatment, the remissions were only transient and incomplete; despite this the drug was pushed in an attempt to secure a worth-while remission. The conclusion we drew from these two cases was that if after a course of T.E.M. sufficient to cause definite depression of the white cells, there is no reasonable remission, it is dangerous and useless to continue with its administration.

The third patient (Case 4 in Fig. 1) benefited considerably from his first two courses, his hæmoglobin rose from 68% to 98%, and a pleural effusion that had needed tapping every three days ceased to accumulate. The third course, however, led to depression of all the formed elements of the blood. ACTH and cortisone have been used for the treatment of bone-marrow depression after chemotherapy and through the courtesy of the Medical Research Council we have had a supply for trial in these patients. A course of ACTH (170 mg. by repeated prolonged intravenous infusions over twenty-four days) was given to this patient; his reticulocytes, white cells and platelets increased and, apart from some anæmia, his blood picture was normal when the course of ACTH was terminated. This may have been a natural recovery from the bone-marrow depression, or the effect of the ACTH. At the end of this course he was still febrile and had evidence of continuing activity of the lymphoma, a further course of T.E.M. was given and an attempt made to prevent the bone-marrow depression by simultaneous ACTH therapy. This was unsuccessful, pancytopenia developed and persisted until his death six months later. During this six months intensive treatment was given with ACTH, cortisone and blood transfusions, but it had little effect on his condition. He felt much better while on hormones and his period of survival was perhaps longer than one would have expected under the circumstances.

The fourth patient (Case 12 in Fig. 1) had an unusually severe and prolonged depression of blood cells and purpura after his first course. This is unusual in a case with recent onset and no previous treatment. The lymphoma responded well to the T.E.M. and when he relapsed three months later a

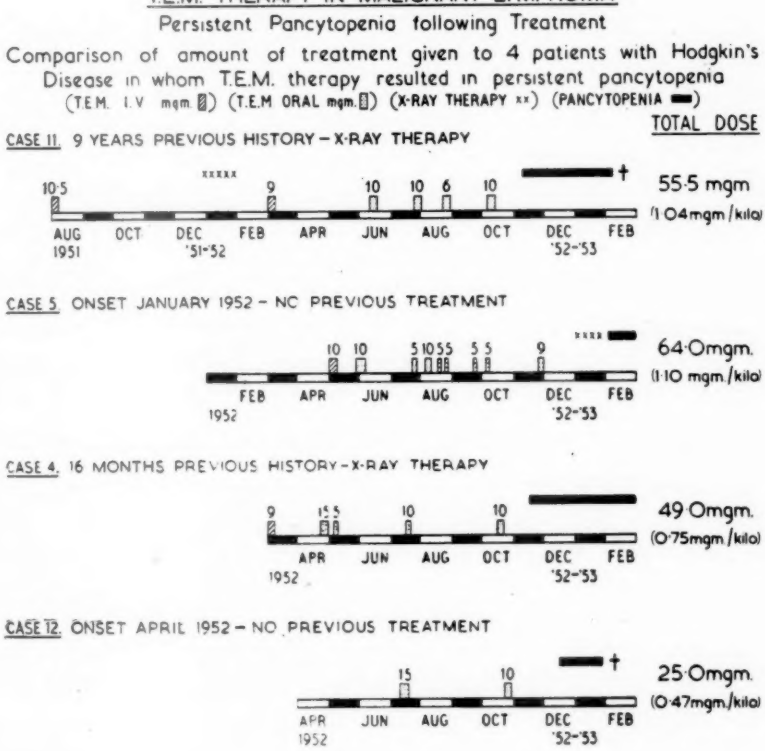

FIG. 1.

further course was given because no other form of treatment was considered practicable. This second course failed to influence his Pel-Ebstein fever and produced a persistent pancytopenia. ACTH had no effect on the lymphoma or the blood condition. It is perhaps significant that at autopsy the bone-marrow was heavily infiltrated with Hodgkin's tissue.

Conclusions

As the result of our experiences to date we have come to the following conclusions. Oral triethylene melamine is an effective palliative agent for patients with Hodgkin's disease. It is indicated in cases showing marked constitutional disturbance or wide dissemination of the disease. At the same time it is dangerous, readily producing aplasia of the bone-marrow and great care is needed in the planning of treatment. The initial course should not exceed 0·2 mg./kg. body weight, but if after ten days the white cell count shows little change a further 0·07 mg./kg. may be given. Smaller doses should be used in patients with any evidence of bone-marrow involvement. If there is evidence of unusual bone-marrow sensitivity following the first course, no more T.E.M. should be given. If the patient shows a definite fall of the white cell count, but only an incomplete and transient remission of the disease, further treatment with T.E.M. is contra-indicated. The drug should be given in definite courses as widely separated as possible, only in exceptional circumstances should a second course be given within two months of the first. There is some evidence that bone-marrow depression is more severe if several courses of treatment are given but further experience is required on this point.

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Section of General Practice

President—E. P. Scott, M.B., M.R.C.S., L.R.C.P.

[*February* 18, 1953]

DISCUSSION ON HYPERTENSION

Dr. Leslie V. Gimson: Hypertension is a common condition which the general practitioner meets almost daily in his work. It is predominantly a disease of the second half of life and therefore, as the expectation of life rises, the proportion of hypertensives among our patients will increase.

By the term "hypertension" I mean a systolic blood pressure (B.P.) of 150 mm. of mercury or more, or a diastolic pressure of 95 mm. or more. For the purpose of life assurance, the maximum readings which will usually be accepted at ordinary rates are age up to 50 years 145/90 and age over 50 years 155/95.

Two main difficulties are encountered in recording B.P. The first is that transient rises of B.P. are very liable to occur at medical examination, especially if the examiner is not well known to the patient. Peripheral vasoconstriction can be caused by nervousness and cold and, therefore, the patient should be kept warm and, if possible, free from apprehension. Despite these precautions, a high systolic pressure will often be obtained at a first examination. Further readings a day or two later, give a lower and more accurate figure.

There has been in recent years, a tendency to attach some importance to these high readings. It is postulated that those in whom a rise in B.P. is produced by nervous strain are pre-hypertensives and that in later years the full syndrome of essential hypertension will develop. It has been said that a systolic pressure of 130 in a young woman at her first ante-natal examination is pathological.

Fear sets in motion the fight or flight mechanism, the signs of which are manifestations of sympathetic activity, tachycardia, dilated pupils, sweating, tremor and a rise in B.P. The last is but one component in what has always been regarded as a physiological process. It may be that further observation will show that a labile B.P. in early life is a prelude to hypertension in later years. Until this fact has been established, however, it appears unwise to attach too much importance to this finding.

A second difficulty in B.P. estimation is that it is not always easy to obtain a clear end point in taking the diastolic pressure. There is not always a sudden change from the sharp sounds to muffled sounds, nor a clear-cut disappearance of all sound.

Systemic hypertension may be divided into primary or essential and secondary hypertension. *Secondary hypertension* is usually due to nephritis, pyelonephritis, polycystic kidney, toxæmia of pregnancy, phæochromocytoma, diabetes mellitus and is found in some cases of thyrotoxicosis and myxœdema. A moderate degree of hypertension is commonly found in the menopausal syndrome and it is convenient at this point to refer to the association between coronary disease and hypertension. Sir Maurice Cassidy in the Harveian oration of 1946, pointed out that in a large series of cases of coronary disease, over one-half of the patients were suffering from hypertension.

Essential hypertension has been defined as a clinical condition in which there is a persistently raised blood pressure independent of renal or arterial disease. The immediate cause of hypertension is increased resistance to the passage of the blood through the small arteries and arterioles due to hypertonus of the plain muscle of the arterial wall. Goldblatt (1951) has shown that in experimental animals, hypertension can be produced by the constriction of the main renal artery of one kidney. In the dog the rise of B.P. occurred within twenty-four to seventy-two hours of the application of a clamp and usually lasted for four to six weeks. Later it was found that in sheep, goats and rats, hypertension lasted much longer as a result of constriction of one renal artery. The constriction of both main renal arteries was followed by hypertension lasting several years. Goldblatt has postulated that in experimental hypertension, the ischæmic kidney produces an enzyme, renin, which enters the blood stream through the renal vein and reacts with hypertensinogen to form hypertensin a polypeptide responsible for peripheral vasoconstriction.

Unilateral renal disease, such as pyelonephritis and polycystic kidney, may cause hypertension and this hypertension may be relieved by nephrectomy, but biopsy of the kidney in a large number of cases of essential hypertension has failed to reveal any pathological lesion.

It has alternatively been suggested that some form of stress may effect the hypothalamus and pituitary which in turn bring about changes in the adrenals resulting in the release of corticosteroids. These are said to act on the renal blood vessels with the production of nephrosclerosis.

Trueta, in experimental animals, has shown that various nervous stimuli may bring about vascular spasm. During the phase of spasm blood is by-passed through the juxta-medullary glomeruli into the renal vein and the renal cortex is rendered ischæmic. Thus renal cortical ischæmia may recur from time to time, due to nervous stimuli and in this way pressor substance may be liberated into the blood stream.

Benign hypertension is of insidious onset with a maximum incidence in the 50 to 60 age group. It is characterized by a diastolic pressure which does not exceed 120, no evidence of cardiac or renal failure, signs in the retina such as silver-wire arteries and symptoms of throbbing in the head, transient giddiness and fatigue on exertion. The onset of *malignant hypertension* is very often in the 40 to 50 age group. Pressure is high with a diastolic reading of 135 mm. or more. The distinguishing clinical sign in malignant hypertension is albuminuric retinitis and the distinctive pathological finding is the presence of acute arteriolar necroses.

It appears probable that benign and malignant hypertension are different phases in the same process and the factor which determines the course of the disease is the level of the diastolic pressure. Professor Pickering and his colleagues (1952) have shown that in albuminuric retinitis the pressure of the cerebrospinal fluid is nearly always above the level at which papilloedema occurs in tumours of the brain and that the pressure seems to be determined, in part, by the arterial diastolic pressure. They have reported 3 cases of malignant hypertension due to pyelonephritis. All showed albuminuric retinitis and acute arteriolar necroses in kidney and adrenals. Operation was followed by a fall in B.P., resolution of the retinitis and conversion from malignant to a benign form of hypertension.

In a large percentage of hypertensives, a family history will be obtained of one or both parents having suffered from the same condition, thus indicating that there is an inherited predisposition to the disease.

Four factors most helpful in the assessment of the prognosis of essential hypertension are: (1) The diastolic pressure reading. (2) Evidence of cardiac failure. (3) Evidence of renal failure. (4) Ophthalmoscopic appearance.

(1) *Diastolic pressure.*—This is probably the most important single factor in assessing the prognosis. The critical level seems to be about 135. Above this figure, the prognosis is bad and a cerebral vascular lesion is likely to occur. With a diastolic pressure of less than 100, the prognosis is good. One frequently sees in practice patients with a pressure of the order of 200/95. This usually indicates a benign condition, the high pulse pressure being due to degeneration of the elastic tissue in the arterial system.

(2) *Evidence of cardiac failure.*—The size of the heart by clinical and radiological examination is an important factor. Dyspnœa on exertion, the presence of fine râles at the bases and an accentuated pulmonary second sound indicate left ventricular failure. An inversion of the T wave in the first and second leads in the ECG is evidence of myocardial strain. Cardiac asthma is a symptom of grave import and a patient rarely lives more than two or three years after its onset.

(3) *Evidence of renal failure.*—Symptoms of uræmia, a raised blood urea and the presence of albumin and casts in the urine, all indicate a grave prognosis. One of the best tests of renal function is the ability of the kidneys to excrete a concentrated urine. This test may easily be performed in general practice. All that need be done is to withhold fluids for twelve hours and then to determine the specific gravity of the urine that is passed at the end of this period.

(4) *Ophthalmoscopic appearance.*—It is necessary to look for the following signs: Uneven calibre of the retinal arteries, nipping of the veins at the arteriovenous crossings, exudates in the retina and papillœdema. A disc and retina which are healthy, apart from a silver-wire appearance of the retinal arteries, are seen in many cases of benign hypertension. In addition to these four factors, the patient's age, family history, occupation, temperament and his habits regarding alcohol and tobacco, must be taken into account in formulating a prognosis.

Treatment

Hypertensive patients may be divided into three groups: *First, those with no symptoms.* Hypertension may be discovered in the course of routine medical examination. If there are no symptoms related to hypertension, no treatment is required and there is no reason why the patient should be informed that his blood pressure is high. *Second, cases in which symptoms are not severe* and the prognosis is good: the symptoms in this group include giddiness, headache, fatigue and perhaps some shortness of breath on exertion. *Third, cases with a high pressure and a bad prognosis.*

Management of Hypertension

There are two essentials in the management of these patients, to allay anxiety and so arrange the patient's activities that he lives within the limits of his capacity with something in reserve. The heart is regarded by laymen as the vital organ of the body. Cardiac and vascular diseases are often accompanied by the fear of sudden death and if the practitioner can dispel these anxieties he will have done his patient good service. In giving a prognosis, it is wise to err

on the side of optimism and when the prognosis is good, as it is in cases of hypertension with a low diastolic pressure, the patient should be left in no doubt that his condition is not serious.

It is inadvisable to tell the patient the B.P. reading.

Adequate rest is important. Nine hours at night and one hour in bed in the middle of the day is to be recommended. Sir Winston Churchill, in his War Memoirs, has drawn attention to the value of "dividing the day's march in two" by going to bed in the afternoon at times when work is heavy and the stress of life severe. This advice can be applied with great benefit to our hypertensive patients. I have found that many patients' symptoms have been very greatly relieved if they go to bed in the middle of the day for an hour. Whenever possible, the patient should go to bed and not simply rest in a chair.

Diet.—A reduction of weight in an obese patient usually relieves symptoms and is sometimes accompanied by a reduction in pressure. Such a patient should be encouraged to follow a diet, but in the absence of obesity, there is no point in imposing irksome dietary restrictions. Before the war, it was a widespread practice to restrict severely the consumption of meat by hypertensives. During the past twelve years, meat has been strictly rationed, but so far it appears to have had little effect on the incidence of hypertension.

There is, as far as I know, no evidence that alcohol or tobacco is responsible for hypertension. If a patient is smoking 30 or 40 cigarettes a day or consuming large quantities of alcohol, a reduction will be beneficial whether he has hypertension or not, but there seems to be no good reason for denying a moderate amount of tobacco and alcohol to our hypertensive patients. Those who believe in ritual purgation advocate the liberal administration of aperients. Provided constipation is corrected and the patient warned of the danger of straining at stool, the alimentary tract may be left in peace. Excessively long hours of work are to be avoided, a period of rest in the middle of the day should be obtained wherever possible. Those employed in heavy manual work may have to find some easier occupation, but as far as possible, patients should be encouraged to follow their normal activities. Drug treatment in this group of patients is usually limited to the prescription of sedatives. Phenobarbitone ½ grain twice daily is of great value in relieving symptoms.

The third group of patients are those with a high pressure and a bad prognosis. There may be severe symptoms, retinopathy or evidence of cardiac or renal failure. A diastolic pressure of over 120 is a cause for anxiety and when it reaches 135 or more, the risk of a cerebral vascular accident is considerable. It is in the management of these cases that a consultant's advice is required. The following are among the methods which may be employed in attempting to reduce these high pressures: (1) Bed rest. (2) Salt-free diet. (3) Pressure-reducing drugs. (4) Surgery.

A few days' rest in bed together with sedatives such as phenobarbitone and Nembutal very frequently reduces the pressure by 10 or 15 mm. and relieves symptoms. A low sodium diet appears to produce a fall in B.P. in about 25% of cases. It is used in the treatment of severe hypertension without evidence of renal failure. A diet containing 2,000 calories and 200 mg. of sodium is suggested. Kempner's rice diet produces 2,000 calories daily and contains 150 mg. sodium. Few patients, however, will tolerate this for long.

Pressure-reducing drugs.—Potassium thiocyanate has a definite hypotensive action. It appears to reduce pressure in about 50% of cases, but has the disadvantage that frequent estimations of the blood level of the thiocyanate must be made. The aim is to maintain a level of between 8 and 12 mg. per 100 ml. blood and a dose of 0·3 to 0·9 gramme daily is usually required. Toxic effects include rashes and gastro-intestinal disturbances. This method of treatment has been largely abandoned.

Ganglion blocking agents.—The halogen salts of hexamethonium and pentamethonium have been extensively used. Good results have been claimed when these drugs are given by injection, but oral administration seems to be unreliable. Toxic effects are common and include pupillary paralysis, nausea, constipation, paralytic ileus and bromism. I have had no success in the few patients I have treated with hexamethonium orally, but it did relieve hiccoughs in a patient with secondary carcinoma of the liver when everything else had failed.

Veriloid, veratrum viride.—I have treated 2 patients with a combination of Veriloid and phenobarbitone. Dosage has been either 3 or 4 tablets daily, each tablet containing 2 mg. of veratrum viride and approximately ¼ grain phenobarbitone. The first was a housekeeper aged 62, who came to see me in May last year complaining of headache and giddiness. Her B.P. was 240/130. With rest and phenobarbitone it had settled by the middle of June to 210/100. At the end of September it was 200/115 and symptoms were still troublesome. I then commenced Veriloid with phenobarbitone. One week later the B.P. was 165/90. Two weeks after this it was back at 190/115 and it remained at about this figure until the end of December when I discontinued the Veriloid as the patient was complaining of tinnitus. The second was a man aged 50. When I first saw him in January 1949 with a B.P. of 190/135, his symptoms were not severe. There was no evidence of cardiac failure and he was at work as a shop assistant. On account of his high diastolic pressure, I thought he might be a candidate for surgery. This, however, he refused. He continued at work with shortened hours and a good interval for rest

in the middle of the day. His pressure varied between 210/130 and 170/110. On one or two occasions, the diastolic pressure reached 140 and I then insisted on a few days' rest in bed which brought the pressure down. In this way he continued until February 1952, when he had a cerebral thrombosis. His blood pressure remained at much the same level until September last year, when the diastolic pressure was 150. Fearing a further thrombosis, I put him on Veriloid with phenobarbitone. I continued this until the end of the year. His diastolic pressure did not rise above 120 during December, but the 14th day of January, it was again 210/140. It is difficult to decide when Veriloid therapy achieved anything in this patient. I have a record of blood pressure readings over four years and similar falls in pressure occurred when the patient was simply having phenobarbitone twice daily.

Surgery in essential hypertension consists principally of some form of sympathectomy or subtotal adrenalectomy with local denervation. As far as I understand, the indications for surgery are:

(1) The patient should be under 50 years of age.

(2) The diastolic pressure and ophthalmoscopic appearance should indicate a bad prognosis.

(3) There should be no evidence of cardiac or renal failure. (It would seem that a young woman with malignant hypertension is the most suitable subject for surgery.)

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Dr. Geoffrey Bourne: *Clinical Varieties.*—The first point in the diagnosis of hypertension is to differentiate the common variety, essential hypertension, from other types of raised blood pressure. Coarctation of the aorta although rare must never be forgotten, especially if a raised B.P. should be found in a young subject, because it can now be dealt with surgically. When this is suspected the abdominal aorta and the femoral vessels should always be palpated, and if vigorous pulsation is absent the B.P. in both arms and legs should be taken by palpation. Estimation of the figures by auscultation is less reliable here since this method is not as easily applicable to the legs as to the arms, whereas palpation of the radial and dorsalis pedis pulses is a strictly comparable measure. Renal disease must next be excluded and a history of scarlet fever or severe sore throat followed by a period of ill-health is suggestive. Albumin, red blood cells and casts may be found in the urine, and renal function tests may be confirmatory.

The spasmodic factor in hypertension is of great importance. It very often gives an exaggerated reading when the patient is first examined. The presence of tachycardia and of the general state of the patient's emotional response to examination will give indications as to the probable extent of such nervous spasm. In young normal but nervous people the B.P. is often similarly raised, the systolic far out of proportion to the diastolic.

Essential hypertension proper may give rise to various clinical pictures. In its most harmless form it causes an increase in the blood pressure during the fifties or sixties and the pressure may remain raised for ten, twenty years or more, the patient remaining free from serious complications. Another relatively harmless variety is that in which the raised pressure is discovered in the twenties or thirties, such patients remaining free from symptoms until they reach the age of vascular atheromatous degeneration. Here again a period of twenty or thirty years of comparatively normal health may end in a more serious cardiovascular accident due to the atheroma rather than to the hypertension. In other patients the rate of progress or development of hypertension may be more rapid still, the whole course lasting a few years only. Finally so-called malignant hypertension may supervene in a more chronic type of the disease, the chief characteristics of this condition being a high and rapidly increasing hypertension, a diastolic figure generally over 130, a grade IV retinitis with papillœdema, and very often evidence of renal insufficiency.

There are thus two factors in all cases. There is the unknown factor, possibly identical with renin, as described in the experiments of Goldblatt and others, which is ultimately responsible for spasm, hypertrophy, and sclerosis of the plain muscle of the media of the smaller arteries and the arterioles. This would seem to be the typical lesion of continued hypertension as such. The second factor, which clinically is perhaps of more importance, is the state of the larger blood vessels with regard to the presence of atheroma. In coarctation of the aorta it is a significant fact that patients live for many years without symptoms of cardiovascular complications, presumably because these cases run most of their course during the period of life when atheroma is rare or non-existent. This second degenerative factor may also be influenced by the presence of such conditions as diabetes and other unknown metabolic states.

SYMPTOMS

The symptoms of hypertension can be divided again into two classes, "metastatic," that is derived from sources outside the patient, such as popular magazine articles, unnecessarily nervous

doctors, and the tragedies of the patient's own family history. The second group which can be directly explained by the hypertension itself are headache, fatigue and insomnia. Examples of symptoms which are found in hypertensive patients, but which are not due to hypertension as such, are headache, due to such causes as occipital fibrositis, migraine, sinusitis, anæmia and to a nervous feeling which can be described as head consciousness; for the hypertensive patient is as much aware of the possibility of strokes, as the cardiac patient with a left chest ache is of angina. Giddiness is another metastatic symptom in many cases. It may be vestibular, and primarily due to some degree of arteriosclerosis affecting the blood supply to the middle ear. In other patients it is vasomotor and results from the fact that in the standing position the blood pressure drops unduly.

The heart is affected in hypertension in three quite distinct ways. The only change may be one of slow progressive hypertrophy of the left ventricle, with no pathological involvement of the coronary blood supply, and with no deterioration of the heart muscle. This is found in patients who have had chronic hypertension for many years without symptoms of any sort. The heart is here very little enlarged. The second variety is true hypertensive heart disease in which medial sclerosis occurs in the small vessels to a considerable and increasing extent, this change causing widespread fine fibrosis and myocardial degeneration throughout the heart. Here the outlook is poor, the prognosis averaging about two years from the onset of cardiac symptoms. Such hearts become progressively enlarged and the patient suffers from the usual symptoms of increasing left ventricular failure. The third cardiac complication is coronary atheroma which may show itself either as angina of effort or as cardiac infarction. The heart here tends to be not so greatly enlarged as in the preceding variety and the outlook is frequently considerably better. True hypertensive heart disease and ischæmic or coronary heart disease may, of course, co-exist.

The sensible clinical approach in any case of hypertension is a thorough and full history and physical examination in order to try to find some other cause for the symptoms than the hypertension itself. This is the method which will bring most good to the individual patient. The second approach is to try to assess and discount the nervous factor in the case. Finally, it is the physician's duty to try to reassure the patient to the maximum justifiable extent. By repeating the complete examination after successive intervals of six months or so it is possible to obtain points on the graph of the patient's life and so to estimate the progress or absence of progress of the disease. The measurements which should be specifically made at the time of the clinical examination are: the diastolic and systolic B.P., taken after the patient has been resting flat on a couch for a quarter to half an hour; the exact size of the heart as measured by orthodiagraph; the state of the left ventricular muscle as estimated by the vigour of the cardiac impulse, the quality of the first sound, the loudness of the aortic second sound and the electrocardiogram; finally the degree of retinal arteriosclerosis, as defined by the four grades now commonly accepted. The next point is to try to assess the amount of atheroma present in the larger arteries as judged by the family history, the presence of angina of effort or intermittent claudication, the condition of the peripheral vessels, and the presence of diabetes, or a family history of it.

Treatment

Symptomless non-progressive cases need no treatment. If progress is slow a full investigation should be made into the habits of life of the patient both as regards occupation and as regards travelling to and from work. The patient should be allowed, and indeed encouraged, to continue as active a life as will not produce serious fatigue. When it is possible a rest should be taken, lying flat for an hour after lunch. Sitting in a chair is not satisfactory, the rest must be taken on a bed or a couch. Obesity should be reduced by diet, and as salt-free a regime as possible should be instituted.

More active hypotensive measures may sometimes be necessary. Strict rest in bed for two or three weeks is essential as a preliminary method of treating malignant hypertension. The hypotensive drugs, whether of the hexamethonium type or of the veratrum viride variety seem to have their place, but they do not seem to have supplied the full answer to the problem. This is not only because of the presence of side effects, but because the hypotensive action, even if it is good to begin with, so often wears off when the patient resumes a more active life. Sympathectomy seems still to have a definite place and indeed it appears to be the only measure which will produce a lasting effect. It is, however, exceedingly difficult to foretell whether such an effect will follow the operation.

A follow-up of 26 cases at St. Bartholomew's Hospital, observed up to a period of five years, would seem to suggest that the indications for surgery are as follows:

The hypertension must be a true progressive hypertension.

The severity of the condition must be considerable, the diastolic pressure being 120 or more.

The age of the patient should be nearer 40 than 50, and other measures of treatment should have failed.

A separate indication is the presence of severe malignant hypertension in which the retinitis is so far developed as to threaten the patient's sight. Sympathectomy here frequently seems to cause very great improvement in vision, even although the ultimate effect as regards prolonging life remains in such cases poor.

There is no doubt that sympathectomy, when it works, lowers the B.P., in a few cases permanently, may reduce the size of the heart measurably, will eliminate the changes of left ventricular stress or hypertrophy from the electrocardiogram, and may benefit greatly advanced cases of severe retinitis.

Mr. Peter Martin: *Operations on the Sympathetic Nervous System.*—It is now nearly twenty years since surgery took a part in the treatment of essential hypertension and it has directed its endeavours in the main to ablation of lesser or greater portions of the sympathetic chain. I will confine my observations to operations on the sympathetic nervous system. The scope of operation, starting modestly with a bilateral lumbar sympathectomy, has now settled to an excision of the chain from T.5 to L.3 together with the splanchnics, and there is no reason to suppose that increased operative technique or scope will increase its effectiveness. Finality as regards sympathetic operations has been reached. Medical treatment by many of the present-day drugs has also been concentrated on paralysing the sympathetic nervous system: both in surgical and medical treatment the results have been disappointing. The reason is, of course, that there is nothing known of the essential pathology, and efforts directed towards sympathetic paralysis are merely like treating abdominal pain by morphia. Methods of achieving sympathetic paralysis in the limbs have been shown at Hammersmith Hospital to be markedly effective for only a few days, and at the end of the week or two to result in only twice the pre-operative blood flow. It may well be that a similar mechanism operates in the splanchnic bed, thus accounting for the fairly rapid return of the B.P. following an initial, apparently successful result. We have heard of the varied success of the drug treatment of hypertension, and the previous speakers have emphasized the common-sense approach to a moderate symptomless hypertension, found generally by chance, and there is no place for surgery in this type of case. It is a curious fact that following a sympathectomy for hypertension with symptoms, these symptoms are cured in something over two-thirds of the cases, in spite of the fact that there may be no great fall in the diastolic B.P. Eye changes regress to an astounding degree, the heart shadow decreases significantly, the patient loses his headaches and dizziness and can concentrate on his work and enjoy his life once again. Patients are, in fact, grateful. In something under one-third of cases B.P. is reduced significantly, though whether this reduction persists for more than ten years I am doubtful.

The case suitable for surgery is the hypertensive with severe symptoms, with no evidence of marked renal embarrassment, preferably under 45 years of age. I have, however, operated on patients of 55 years with resulting improvement in symptomatology and even useful reduction of pressure. These had a labile B.P. shown by reduction to near normal as a result of deep sedation with sodium amytal. For the sedation test, this must be repeated in 3-grain doses hourly until the patient cannot readily be roused. We are, however, insisting less on a positive result from this test and are not quite certain of its significance. Moderate cardiac failure is not necessarily a contra-indication, nor is minor cerebral complication. Malignant hypertension—and a diastolic pressure of more than 130 mm. mercury is a good indication for its diagnosis—should not in the first instance be treated surgically, although there may be a place for sympathectomy if and when the malignant phase has reverted to the so-called simple phase with drug treatment. There are, however, a few brilliant results of surgical treatment, and operation may be considered where medical treatment is not attended with much success.

A girl aged 7 was subjected to sympathectomy for a malignant hypertension. She was suffering from intense headaches and owing to gross retinal changes could only count fingers. She is now, five years later, head of her class and plays hockey for her school. Her diastolic pressure is 120 mm. mercury, and the prognosis must be poor, but she has had a respite. In similar cases I have had success with a Peet's supradiaphragmatic sympathectomy where the whole procedure could be completed in one operation rather than the two stages necessary in the more extensive Smithwick's operation.

The mortality of operation in properly selected cases is less than 5% but complications such as intercostal neuralgia, rarely lasting more than three weeks, a Raynaud's phenomenon in the hands and excessive sweating may occur following operation.

No simple method of treatment is successful in a large proportion of cases, but I believe there is a distinct place for surgery, particularly where control of hexamethonium drugs is likely to prove tiresome and difficult or where medical treatment has failed. Statistical surveys have shown that operation does lead to an increased life expectancy.

This problem of hypertension will I feel sure be solved by medical rather than by surgical means; but patients must not be refused the benefits of palliation by whatever means, and operation still holds a place of importance in this respect.

JOINT MEETING No. 4

Section of Epidemiology and Preventive Medicine with Section of General Practice

Chairman—E. P. SCOTT, M.B., M.R.C.S., L.R.C.P.
(President of the Section of General Practice)

[*January* 21, 1953]

Studies of a General Practice (I)
Patients' Needs and Doctors' Services: A Description of Method

By E. MAURICE BACKETT, B.Sc., M.B., B.S., M.R.C.P., L. A. SHAW, M.A., and J. C. G. EVANS, M.B., B.S.

Social Medicine Research Unit, Medical Research Council

ACCURATE information is needed about general practice more than about the other branches of the National Health Service. It is now generally agreed that this information could be provided through further research, and that the results might be of use to those responsible for the future of the general practitioner services and as teaching material to be used in the medical schools. Such research, which might be expected to be a major interest of the Central Health Services Council, may well become an important part of the work of the new College of General Practice. At present it lies mainly within the province of academic departments of social medicine.

THE PRESENT STUDY—PURPOSE AND DESIGN

Methods in many studies of medical care have been developed *ad hoc* to deal only with a particular problem.[1] In consequence there is lack of comparability of data and there are few accepted definitions upon which to build further work. Even in the orthodox field of morbidity the diagnoses which are met in general practice can only be fitted with difficulty, and some loss of meaning, into one of the accepted coding schemes. This is particularly the case with symptomatic diagnoses which often reflect no definite pathology.

Methods of describing the G.P.'s job are likely to have more general acceptance, because the number of consultations, prescriptions and other services can be counted, and these terms have much the same meaning wherever they occur. However, to relate such facts to the patients concerned and particularly to the diagnoses which have been made, presents problems to which there are many possible solutions.

The purpose of the present study is to enquire into such difficulties, to investigate some of the methods which can be used in general practice research, and to try them out in the detailed study of an urban National Health Service practice. It is hoped that they will be useful to other workers in this field and especially to general practitioners themselves. The place of such an enquiry as this among studies of medical care is, therefore, primarily among those concerned with *method* and, since only one practice was investigated, to a much smaller extent among those concerned with the *results* of general practice research. Some of these results, however, will be presented in the *British Medical Journal* in the near future.

In this enquiry the medical problems of those registered in a medium-sized urban practice were listed in various ways. This material, concerning the "needs" of patients, was then related to the work of the doctors and other branches of the health services of the district and, of course, to the age, sex and social characteristics of the people concerned. By tabulating this material it could be used not only to gain insight into the extent and quality of the medical care in the practice, but also as one step toward answering more specific questions such as those which follow.

There is an increasingly large literature on this subject, mainly British and American. It is felt that a paper such as this is not the place for the comprehensive review necessary to do it justice.

A. *Questions about the needs of patients:* With what sort of problems is the G.P. concerned? How much serious disease exists among his patients? What percentage of diagnoses fall into various diagnostic groups, such as acute respiratory, or chronic cardiovascular disorders? What proportion of diagnoses are of defined disorders, and what proportion are symptomatic only?

What is the age and sex grouping of his patients with regard to serious and minor diseases, and what is their social class?

What is the nature and extent of the total medical need of individuals, including that which is not treated through the health services?

What is the nature and extent of the social problems associated with the illnesses which are treated by the doctor?

B. *Questions about the doctor's job:* How does the doctor spend his time? How much of his time is spent in the treatment of chronic, serious or trivial disease; where and when are these treated? Which groups of diagnoses involve him in most work?

With what groups of his patients does his main work lie? Do certain classes of patients seem to demand more consideration in treatment than others, e.g. more prescriptions, more referrals? Does a small and definable proportion of patients take up a large proportion of the doctor's time, or does he spread his work evenly between all of them? What are the effects upon the doctor's work of, for example, the ageing of the population?

How many examinations does the doctor make and of what type are they? How many certificates does he give, how many referrals to hospital for diagnosis, for treatment?

How do doctors differ in their ways of working? Why does one doctor visit his patients more often than another, undertake more examinations of a particular kind, or require more diagnostic aids? How are such differences related to the needs of their patients?

C. *Questions about the practitioner's relations with other services:* To what extent do the G.P.'s services overlap with others? If there are gaps, are these due to shortcomings or to poor co-ordination of existing services?

What is the effect upon the patient of the separation of the various health authorities dealing, for example, with mothers and children? How much more co-ordination of these services is possible or desirable?

D. *Questions about family health:* To what extent is it possible or necessary for the G.P. to consider the family as well as the individual in treatment? Are there healthy and unhealthy families and, if this is the case, to what extent are communicable disease factors, family size, &c., responsible? What relationships exist between the social, psychological and economic circumstances of families and their patterns of illness?

E. *Questions about the use of the health services:* What proportion of the health problems which occur in a practice are treated at all, by the family, by the G.P., by the hospital or public health services or by a combination of these? What is the total consumption of health services by various types of families and how well does the supply meet the demand in this respect?

In order to attempt to answer these and similar questions several approaches are necessary.

Records from the Practice

It was decided not to use the doctor's own records of his contact with patients as the main source of information about his job, but to ask him to complete a separate record card after each consultation, wherever this took place. This record card usually took less than one minute to complete. On it were summarized the data necessary to identify the patient and to distinguish the diagnosis which had been made and the services which the doctor had rendered as well as the time and place of the consultation. For a registered population of just over 3,000 persons nearly 16,000 of such records were completed in a test year, i.e. about 100 consultations per thousand registered persons per week.

At six-weekly intervals for one week, members of the unit staff "sat in" on all consultations and made more detailed records. These "intensive" records formed to some extent a control upon the content and numbers of cards completed by the doctors in the practice. They were also a source of additional detail concerning the services rendered in treatment, e.g. the type of examination, the nature of the apparatus used. All this information was transcribed on to another card, one of which was kept for each patient. This material was later classified in various ways and the necessary tables were produced.

A Sample of Ordinary Families

Records of the doctor's work contain information about the patients and the diseases which he treats. This source gives no information about three important aspects of the health of those in his practice. It can give no account of ill-health which exists, but for which advice is not sought from the doctor. Often it can give no account of treatment which has been given but which has not been requested by him (e.g. in hospital casualty clinics, industrial clinics and the like). Moreover, from such records the information that is available is usually about *individuals* and rarely about *families*. Because of these inevitable gaps in the information to be gained from the general practitioner, because of an interest in *all* the needs for medical care and in *all* the services available to meet them, and also because of the importance which is attached to the problems of *family* health, it was decided to make a direct study of a group of ordinary families in the practice.

For this part of the enquiry a case study method was used; home visits were paid to each family by the team's social worker once a month for a period of six months. The purpose was to make a record of the events in the life of an ordinary family which could have a bearing on health and illness, and of what the family had done about them. This naturally included events having a bearing on mental health and illness and in this connection family relationships and attitudes were regarded as within the scope of the study.

Thus, material was available from two main sources: from the health records of the sample families and from the records kept by the doctor. It was expected to become available in terms of (1) the *medical problems* experienced and described by the families, (2) the *diagnoses* made by the doctors and the numbers and the *duration of the episodes of illness*, and (3) the *work and services* rendered in response to these needs.

Analysis of such material depends upon a coding system which in turn must lean heavily upon a series of operational definitions, for example of "serious", of "chronic", &c. After pilot studies a group of definitions was decided upon and these are summarized below.

THE DEFINITIONS WHICH HAVE BEEN USED

(A) *... the Study of the Whole Practice*

(1) *Disease processes, diagnoses and illnesses.*—From the patient's point of view, what takes him to the doctor is a series of symptoms, or a general malaise which lasts for a fairly definite time. This to him is an illness; an episode, or a period of ill-health. What the doctor records as the diagnosis may be anything ranging from a single record of "pneumonia", for example, to the most complicated entry of several diagnoses, each differing in importance. In addition, perhaps, there may be added the diagnosis of a minor deformity which the patient has had all his life but has never noticed. There are here two distinct ideas. The first is the "illness"; the second is the "disease process" or "processes" which underly the disturbance of well-being or are present without such disturbance.

To examine the ideas of *illness* and *disease* in relation to this population it was obvious that a variety of approaches should be tried. From the doctors' point of view two were found to be practical; a review of the diagnoses which were made in the practice, and an analysis in terms of the number of periods of illness which occurred among patients.

Disease processes then, are the pathological processes (so far as they are known) which underly the patient's illness. They are reflected in the 6,000 odd diagnoses which the doctors entered upon their records of consultations during the year. Disease processes were classified in three broad groups as "acute infective", "acute non-infective" or "chronic". Nearly half were acute infections and about one-fifth of them were classified as chronic. They have been further classified by a 28-element diagnosis code (Table I).

TABLE I.—THE DIAGNOSIS CODE

Disease process	Diagnosis code number	Disease process	Diagnosis code number
Nasopharyngitis, coryza, &c.	11	Varicose veins, thrombophlebitis, and complications	24
Influenza	12	Skin sepsis	25
Tonsillitis, pharyngitis, laryngitis, tracheitis, &c.	13	Other skin disease	26
Otitis media	14	Errors of refraction	27
Bronchitis	15	Rheumatism, neuralgia, fibrositis, &c.	28
Chronic bronchitis, emphysema, &c. ..	16	Arthritis, synovitis, &c.	29
Pneumonia, pleurisy	17	Malignant disease, all forms	30
Pulmonary tuberculosis	18	Injuries, and sequelæ	31
Acute specific fevers	19	Functional nervous, psychoneurosis, &c.	32
Alimentary infections, infestations, &c.	20	Acute surgical emergencies	33
Peptic ulcer, chronic or recurrent dyspepsia, and sequelæ	21	Female genito-urinary*	34
		"Anæmias"	35
All organic cardiovascular disease (except 23)	22	Other defined disorders	36
		Undefined, symptoms only, unclassified, &c.	37
Hypertension and complications, chronic nephritis and complications	23	Dental	38

*Pregnancy is classified with 34

Four considerations guided the construction of this code. First, it was held to be important to be able to move data easily from the selected code to other codes more widely used. Second, with certain exceptions which were of special interest, such as cancer, tuberculosis, hypertensive heart disease and neurosis, each category should accept enough of the diagnoses to make manipulation of the figures possible; and third, the categories used should be related realistically to the phrasing of general practitioner diagnoses. Finally, it was decided that the code (excluding "other defined disorders") should accept at least 90% of all the diagnoses made.

An *illness* is the disturbance of the patient's health which is reflected in at least one consultation. This episode may be a first appearance, a recurrence, or an exacerbation of one or more disease processes. Since it refers to the *whole* disturbance of the patient, it follows that only one illness can occur at one time. Illnesses have been classified in four groups by reference to the disease processes which they "contain" and to their *duration*, being either acute infective illnesses, acute non-infective illnesses, chronic illnesses or "mixed" illnesses with disease processes from more than one of these groups underlying them.

(2) *Duration.*—Certain disease processes were defined as "chronic" regardless of their apparent duration. These were such obvious conditions as tuberculosis, cancer, hypertension, peptic ulcer and varicose veins. Other conditions were defined as acute in the same way; these were such conditions as the acute specific fevers, coryza and influenza. The remainder were only classed as chronic when there was evidence of duration of three months or more.

(3) *Seriousness.*—This has proved one of the most difficult and important definitions and has, as its basis, the idea of an imminent threat to the life or livelihood of the patient or the need for a major readjustment on his part or that of the family. Where this evidence did not exist the condition was classed as "not serious". Certain conditions, however, were assumed to be serious even in the absence of evidence. These were such conditions as acute surgical emergencies, pulmonary tuberculosis, cancer and peptic ulcer.

It was recognized that by invoking in the definition of serious disease its social repercussions, more "serious" disease than might be expected on the basis of pathology alone would be found. However, the large majority of such "serious" diseases were in fact found to be based upon important organic pathology. The reality of this approach has been strengthened further by reference to the study of the sample families where more certain and corroborating evidence was obtained of the seriousness of some of the conditions about which there had previously been doubt. About one-sixth of all the diseases met by the doctors were classified in this way as "serious". If an illness "contained" a serious disease it also was said to be "serious".

(4) *Work.—The consultation* has been used as the basic unit of the doctor's work and includes all types of clinical contact, even chance meetings where advice is sought or given, telephone conversations, meetings in hospital, &c. These consultations have been described according to the *seriousness* of the disease processes which are involved and the *duration* of the illness of which they were a part, and also in terms of the characteristics of the patients and the time, place and doctor involved.

The services (prescriptions, examinations, referrals and the like) have been classified and counted in the same way as the consultations in which they took place.

(B) *In the Study of the Sample of Families*

(1) *Medical problems.*—Some difficulty was experienced in classifying the material derived from the families' own description of their health. For example, when it was reported that since the previous interview a member had been ill with "influenza", this was treated as information about a medical problem, of which only the seriousness and duration could be known or estimated with reasonable accuracy. There was, of course, room for doubt about the accuracy of the *diagnosis* when there was no corroborating evidence available from the doctor's records. Again, if a condition such as a mass in the breast had been reported in the course of an interview with a family it would have been coded as a medical problem regardless of whether the person or family concerned regarded it as such. Where a decision was difficult (for example with certain medico-social problems such as separation or bereavement), guidance as to what was a "medical problem" (and which was, therefore, potentially at least, the responsibility of the health service) was gained from a review of what the doctor himself would have regarded as his "duty" to treat, *if the problem were encountered by him.* Among 101 families (339 people) who took part in this study during six months, there were reported 814 of these "medical problems".

(2) *Seriousness and duration.*—The same definitions as were used in the classification of data from the whole practice were invoked in describing the medical problems of the sample of families.

(3) *Trivia.*—This term was used to describe the small "tail end" of the list of medical problems ranged according to their seriousness. It embraced only those in which there were, of course, no serious implications, which were of less than one week in duration, which carried no further threat of ill-health and were self-limiting and where it was considered that no treatment by a doctor was necessary. Such were "colds" and minor abrasions, transient headaches and the like. "Ordinary" health problems were those not coded as serious nor yet considered "trivial".

The Present Study—Procedure

Describing the Population of the Practice

Any investigation of a general practice must of necessity describe the population "at risk". The minimum information which was felt to be necessary was the age and sex of those registered with the practice and information as to their occupation and civil state.

The occupational data on each individual were collected as a basis for classification by the Registrar General's five social classes.

In order to get this basic information every registered person was approached by letter and asked to give his age, occupation and civil state. A surprisingly large number of replies were available immediately, and after several further attempts and a series of visits to their homes the small remaining number of persons about whom no information was available was reduced to 1·7% of the average population (3,084). In the course of this description of the population it was necessary to compare the *real* size and composition of the practice with the *records* of its size and composition at the local Executive Council and in the practice itself. It was found that these estimates differed considerably, in the way summarized in Tables II and III.

Table II.—The "Inflation" of the Practice Records
N.W. London Practice, April 1950

	Individuals registered and found to be present	Individuals registered according to the Executive Council	Individuals registered according to the Medical Record Envelopes held by the doctor
Number ..	3,037	3,483	3,611
% excess ..	—	15%	19%

Table III.—The Situation of Persons Represented in the Practitioner's Records But Not Accounted for in the Practice
N.W. London Practice, April 1950

Outcome of search for "missing" persons	Number of persons	% of total (3,037)
Found to have died	59	2
Found to have transferred to another doctor's list ..	178	6
No trace in district or on local doctors' lists	284	9
Found to have been represented by duplicated cards ..	53	2
Total of "missing" persons	574	19

Much of this "inflation", which was large enough to distort seriously any analysis of practice records, was due to the disruption of the population in the area during the war, but a small amount had obviously been in existence for many years prior to the big population movements of the early war years. The authors understand that since 1950 new procedures have been introduced to reduce this kind of inflation in the lists of doctors' patients.

Selecting the Sample of Families

Many people on a doctor's list will be found to be related to each other and all members of these *family groups*, in compact areas, may register with the same family doctor. Although an arrangement such as this will help the doctor a great deal, it is not always found to be the case, and for some groups there are almost as many doctors attending a family as there are related persons in it (in one family which was interviewed, the five members were attended by four doctors—perhaps an unusual measure of safety).

In this study it was decided to sample only the families (defined as related persons living at an address) in which all persons were registered with the practice and to work with 100 of these in the investigation of family health through home visits. Only such "complete" families were chosen since full medical data would be available for all their members and because of the importance which was attached to confining the study within the one practice. From the medical record envelopes it was possible to sample households, but there was, of course, no evidence as to whether *all* the members of such households were registered with the doctor concerned, nor was it possible to obtain this information from any official source, for it does not exist. In order to establish the number of households in which every member was registered with the one doctor, a survey was necessary. By the use of random sampling numbers, 250 addresses were selected from the 1,128 separate addresses on the doctor's list. Thus one household in 4·5 was selected for study. These households were visited and the *size* of the family, the *names* and *relatedness* of the persons living there, were noted. From this information and that derived from an additional small sample (needed to get sufficient numbers) it was possible to decide the extent in the practice of "completeness" or whole family registration with the one doctor. The result of this survey is summarized in Table IV.

TABLE IV.—THE EXTENT OF WHOLE FAMILY REGISTRATION WITH THE PRACTICE

N.W. London Practice, 1951

Definition of "family"	Percentage of "families" In which the whole "family" was registered with the doctor	In which the whole "family" was not registered with the doctor	Total Per cent	Total Number of such "families"
A group containing at least a mother and children	96	4	100	105
Parent, or parents with children. Married couples	60	40	100	201
All related persons living at the same address	47	53	100	229
Families with children *and* other relatives living at the same address	27	73	100	37

NOTES.—(1) Many of the above families are, of course, represented in more than one group.

(2) In the main sample 250 *households* were selected and of these 227 were interviewed satisfactorily. In the 227 households it was found that there were 257 *families* (defined as related persons living at an address).

(3) All these definitions of the family exclude, of course, the single person living alone.

It will be seen that the general practitioner, in this practice at least, can hope to be a family doctor to only about 60% of his families, defining them in conservative terms. More liberal definitions, that of the "extended family" for instance, which includes relatives other than children, husbands and wives, but is still confined to the address, restrict the possibility of "family doctoring" still further. When, however, the records of 105 groups of *mothers and children* were examined it was found that in all but 4 cases each of these "family nuclei" was being served by the one doctor.

From all the "complete" families, a further group was selected at random from which, on the basis of pilot studies, it was expected that 100 families would emerge as full participants in the "family health" part of the study. 134 families were selected and of the 117 which were approached, 101 co-operated in the study.

More information was gradually built up about this group of families. Their age, sex and social class were already known and with their co-operation it was soon possible further to describe them in terms of the duration of their stay in the borough, their housing, and an estimate of their economic prosperity, &c. As the visits of the social worker progressed, additional material was gathered about the social functioning of the families. This type of information became available through the establishment of a friendly relationship between the social worker and the families; a relationship not entirely one sided since she was able to offer casework help to a few of them in her professional capacity when the need arose.

Describing the Doctor's Work

Probably the best way to describe quantitatively the G.P.'s job is in terms of the number, length, seriousness and type of illnesses the treatment of which he supervises, and of the extent of his responsibility for this supervision together with the number and type of services and patients which are involved. For example, in this study over 40% of the work of the practice involved "serious disease". A large proportion of this "serious" work was with disease of long duration, and again, much of this, of course, was work with the elderly patients in the practice. One difficulty in this otherwise straightforward operation (which, of course, can be taken in detail much further than in the example) concerns multiple diagnoses. It was found to be almost impossible to relate

consultations and services (the doctor's work) directly to individual diagnoses because, when there was more than one diagnosis, this would entail fractions of such consultations and services being "allocated" to each. For this reason it was not possible to give the precise number of these consultations, prescriptions and the like which were concerned with, for example, skin sepsis, except where it was the only diagnosis made at the consultation. The exact proportion of all of the doctor's work caused by skin sepsis was likewise impossible to state, but the range or limits between which this proportion lay could be shown with some accuracy. This was done by dividing all consultations into (*a*) those where skin sepsis occurred on its own, and (*b*) those where it occurred together with at least one other diagnosis. (*a*) and (*a*) + (*b*) (the minimum and maximum numbers of consultations involved) could then be expressed as the proportion of all the work of the practice. For example, skin sepsis when it occurred *alone* involved 512 consultations, or 3·2% of all the work. Altogether, however, skin sepsis featured in 1,064 consultations, or 6·7% of the work of the doctors in the year.

The average amount of work to be expected with each patient of any given age may be calculated easily. It is likely to be more helpful in the understanding of the doctor's job, however, to consider how the work is *concentrated* among patients, and this is shown by the frequency with which individual patients consult their doctor. In this way the 25 or 30% of persons who are registered but who never seem to consult their doctors at all (and who therefore cause him no work), can be contrasted with those (about 1 out of every 25 persons) who consult about twenty-five times in the year, and who therefore are the cause of a disproportionately large amount of the doctor's work.

Describing the Treatment of Medical Problems Encountered in the Home

In addition to analysing the doctor's services to the patients who consulted him, the treatment of *all* the "medical problems" encountered among the sample of families was also investigated.

As each medical problem which had been reported by the families was considered and its *duration* and *severity* coded, a *treatment* code was added which was based upon records which had been checked with the various agencies concerned and which described its treatment.

Through these classifications, an estimate of potential and actual consumption of health services became possible; for example it was possible to see how much respiratory illness in any given age group or family type was receiving treatment and how much was not. Further, each problem was classed as either "serious", "ordinary" or "trivial" according to operationally defined criteria, and its duration was known. Thus the extent, type and implications of the *unmet* need still existing among these families could be described. Finally, since the age, sex and social characteristics of the individuals in the families were also known, it was possible to say among what sort of people and families this unmet need existed. An important example of the use of these classifications is in the field of *mental illness*. All the medical problems encountered among the families which were of this type (defined, of course, in as much detail as possible) were grouped in the way described above. It was then found that only a relatively small proportion of these problems was dealt with through the health services and that an appreciable number of those which were not treated at all had been classed as "serious". The type of family and the age of the patient in these cases served to define further the importance or otherwise of this unmet need.

The descriptive material obtained by the social worker at her interviews will help to explain, or at least further to describe, the factors which determine the manner in which these "medical problems" were treated and when their presence was first recognized. Such are the attitudes and feelings of people towards their doctors, the health services and their hospital; factors which determine the "threshold" beyond which they must be disturbed in order to recognize the existence of ill-health.

Summary

The methods which have been used in the study of a National Health Service practice of about 3,000 persons in N.W. London are described and some of the main problems which were encountered are discussed. The enquiry has had two main parts. In the first the work of the doctor and the medical needs of his patients were studied and measured by means of records of the 16,000 consultations with patients and the 6,000 diagnoses made by him during a year. In the second, a random sample of 101 families from the practice was visited for six months by a social worker. From her records of the 800 medical problems which she encountered and those of the G.P., the hospital, and the Public Health Service, estimates were made of the extent of the *total* medical needs of the families and of the treatment which was obtained. Definitions which have been used in the classification of material from both parts of the study are discussed and the *diagnosis code* which was the basis of the classification of diseases is given. While gathering information about the registered population it was found that the records held by the Executive Council were 15%, and the doctors' own records were 19% in excess of the number of persons actually present in the practice. The method is described whereby the random sample of families was selected for special study and the difficulties of selecting only those in whom all members were registered with the one doctor are discussed. It was found that only about 60% of the families in the practice were of this type. Questions about general practice which might be answered by the further tabulation of this sort of material are listed.

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Clinical Section

President—HAROLD EDWARDS, C.B.E., M.S.

[*March* 13, 1953]

Tuberculous Palmar Ganglion—Disappeared in Three Weeks under Antibiotic Treatment.—R. H. METCALFE, M.D., M.Ch., F.R.C.S.

K. W., male, aged 26.

Family history.—Sister and girl friend in sanatorium—both with pulmonary tuberculosis.

Patient's past history.—1949: Jaundice for eight weeks. 1951: Right pleural effusion. Pleural fluid straw-coloured; W.B.C. 2,000; numerous lymphocytes; culture sterile. Mantoux test positive 1 in 10,000.

History of recent illness.—21.11.52: Seen as out-patient at St. James's Hospital. History of four weeks' swelling of palm of left hand and anterior aspect of lower forearm (typical appearance of palmar ganglion).

Biopsy (5.12.52).—Tendon sheath swollen and very œdematous and covered with yellow tubercles. Section showed tuberculous granulation tissue. Wound healed by first intention in ten days.

Treatment.—Plaster of Paris back slab. Intramuscular injection of streptomycin sulphate 0·5 gramme b.d. PAS 12 grammes daily in six spaced doses. Isoniazid 200 mg. b.d. These drugs were given for a period of ninety days with a view to prevention of resistant strains of tubercle bacilli.

Swelling of palm and forearm disappeared completely within three weeks of commencement of chemotherapy and the patient returned to his work as a bricklayer three and a half months after commencement of treatment.

Cyst of Tongue.—GEOFFREY PARKER, F.R.C.S.

Male, aged 32.

History of an intermittent swelling at the back of the tongue followed by a discharge of a jet of mucoid fluid from a small sinus in the mid-line of the tongue, anterior to the foramen cæcum. Sialogram shows that this sinus communicates with a cavity about the size of a cherry in the centre of the tongue musculature.

This is, in fact, the lingual element of a thyroglossal cyst, a rare condition, of which less than 2% are reported from the Johns Hopkins Institute out of 105 thyroglossal cysts and sinuses seen over a period of ten years. The patient also states that a lump appears "over his Adam's apple" and a linear thickening in the mid-line can be felt in this position.

In view of the high recurrence rate from inadequate surgery on this condition, it is proposed to remove the tumour through a transverse incision in the sub-mental region and also to trace up such thyroglossal elements as may be found between the hyoid bone and the cyst in the tongue.

Mr. H. H. Renyard: I have seen in the last few months an infant with a tumour similar to the one shown, just in front of the foramen cæcum. The child also had a true gastric cyst with pancreas at its edge in the neck. Section of the tumour of the tongue showed it to be an ectopic salivary gland with a duct which led on to the surface of the tongue. I would suggest that some of the fluid is collected from this patient and examined biochemically for saliva.

Mr. M. R. Ewing: I am confident that this is a thyroglossal remnant. The nodular area that one can feel in the sub-mental region certainly supports this diagnosis. I would strongly advise making a simultaneous approach through the neck and through the mouth in order to ensure a complete excision of the whole track.

Mr. R. H. Franklin advocated an operation from the neck on the grounds that a downward extension of the thyroglossal duct was probable, and that it was important to remove the body of the hyoid bone in these cases.

POSTSCRIPT (16.7.53).—The cyst was operated upon two weeks ago through the usual transverse sub-mental incision. Fibrous elements having the appearance of duct remnants were traced upwards from the hyoid bone into the base of the tongue and at this point the cyst was found and opened. It contained thin pus. The cyst wall was removed and is reported as containing squamous epithelial elements and round-cell infiltration of the surrounding tissue with many typical tuberculous giant cells.

Progress.—Recovery was uninterrupted. The neck wound healed soundly. On discharge from hospital there remained a slight area of induration in the region of the foramen cæcum, but no further discharge in the mouth.

The pathologist had no doubt that it was a thyroglossal cyst with superimposed tuberculous infection.—G. P.

Stricture of Small Intestine.—R. H. FRANKLIN, F.R.C.S.

J. B., aged 10 years.

History.—August 1948: Started to have colicky abdominal pain and vomiting. Mantoux reaction negative. November 1948: High temperature, vomiting and pain. Abdominal tuberculosis diagnosed. May 1950: Severe abdominal symptoms, pain, vomiting and signs of obstruction. Laparotomy showed a severe plastic tuberculous peritonitis. Tubercle bacilli not demonstrated. Mantoux reaction negative. June 1951: B.C.G., streptomycin and PAS given with improvement. From November 1951 to January 1952 deterioration with vomiting, steatorrhœa and gross wasting. Chronic intestinal obstruction. Weight 2st.

27.2.52.—Laparotomy (R. H. F.): Gross distension of the small bowel; half-way along there was an annular constriction. A side-to-side anastomosis was performed. Good recovery and gain of 2 st. in weight.

30.4.52.—Laparotomy (R. H. F.): The annular constriction and the anastomosis were excised and end-to-end anastomosis done. Good recovery and further gain in weight.

The excised portion of intestine showed two strictures. Section showed fibrosis with no evidence of tuberculosis and one small mass of tuberculous follicles in one lymph node.

Neurosarcoma Following Neurofibromatosis.—H. H. RENYARD, M.S. (for HAROLD EDWARDS, C.B.E., M.S.).

History.—Boy aged 17 with a generalized neurofibromatosis, café-au-lait patches and multiple subcutaneous nodules. No family history. He was a high-grade mental defective, and in 1949 a fibrosarcoma was removed from the right buttock by Sir Stanford Cade, followed by radiotherapy. In September 1952 a further tumour appeared on the outer side of the right thigh. This was removed by Mr. Harold Edwards on 30.1.53 and found to be an oval mass attached to the right vastus lateralis. All the nerve trunks which were exposed at this operation contained small grape-like masses, one of which was detached for section. Section showed the larger mass to be a cellular neurilemmoma with no absolute evidence of malignancy. The picture was, however, confused because of radiotherapy to this tumour a few weeks before operation. Section of the smaller tumour showed it to be a neurofibroma. A further lump has now appeared behind the left knee.

On examination.—The skin contained the typical pigment associated with neurofibromatosis. There were many subcutaneous nodules, some of them painful, to be felt on the limbs and trunk. There was a healed wound of the right buttock and right thigh. There was an oval swelling at the upper end of the left popliteal fossa deep to the biceps femoris.

Discussion.—Sarcomatous change in the nodules of neurofibromatosis is said to occur in 10 to 15% of patients. This is probably too high a figure, since there are many minor degrees of this disease which are never seen at all. Some members of a family may present pigmented patches only, while others, at the other end of the scale, develop plexiform neuromas, gliomas and meningiomas.

The origin of these tumours still taxes histologists, pathologists and embryologists. The neurilemmal sheath is thought by some to arise from the neural crest; others consider it to originate from the mesoderm. In the section of the specimen from the present case there is much collagen, but this does not prove mesodermal origin. In fact there are all grades of nerve sheath tumours from true neurofibromas to neurilemmomas, and the malignant variety show similar variations. All authorities are agreed that these tumours are radio-resistant.

POSTSCRIPT.—Since this patient was shown at the meeting a further X-ray has revealed that he now has secondary deposits in the chest.—H. H. R.

Mr. R. H. Franklin recalled 2 such cases. One was a young man who had had multiple neurofibromatosis for many years and then developed a fibrosarcoma in the popliteal fossa. The other patient was a woman who presented with a unilateral proptosis, and the true diagnosis of multiple neurofibromatosis with a probable malignant change in a retro-orbital neurofibroma was not made until a neurological colleague noticed that the patient had patchy pigmentation on the skin.

Mr. M. R. Ewing: We were confronted only this morning in the Postgraduate Medical School with a case of this sort. The sarcoma in this case originated in the mediastinum and presented as a Pancoast syndrome. It is interesting that the patient's granddaughters, who are twins, are blind or nearly so.

Type 2 Nephritis Relapsing Thirty Years After Onset, with Two Full-term Pregnancies Occurring During the Course of the Disease.—H. G. L. LLOYD-THOMAS, M.R.C.P. (for Professor M. L. ROSENHEIM, F.R.C.P.).

MRS. E. S., housewife, aged 44.

History.—1923: Aged 14. Generalized œdema with ascites and pleural effusions lasting for eight to ten weeks. No preceding throat infection. No hæmaturia. Blood pressure 112 mm.Hg systolic. Albuminuria up to 40 parts per 1,000. Blood urea 36 mg.%. Treatment with low salt diet and diuretics was not successful in reducing the œdema. Left renal decapsulation was undertaken, with biopsy.

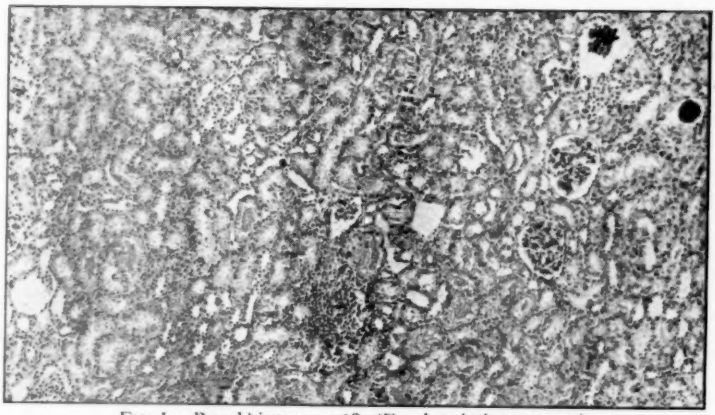

FIG. 1.—Renal biopsy. × 60. (For description *see* text.)

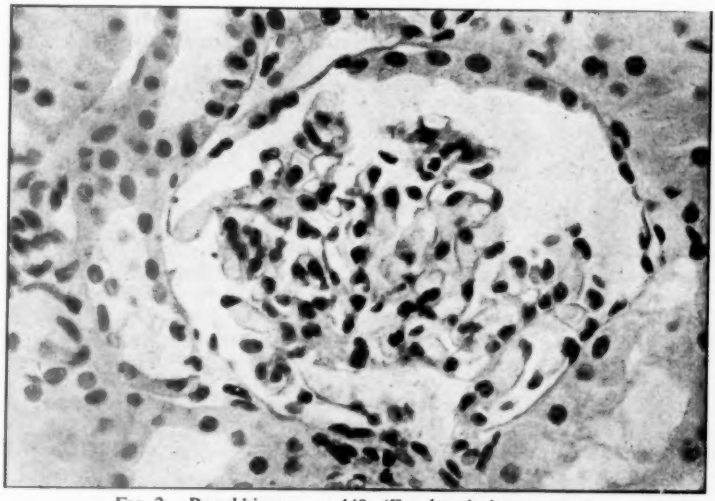

FIG. 2.—Renal biopsy. × 440. (For description *see* text.)

Renal biopsy (Figs. 1 and 2).—Some glomeruli are more cellular than normal, the parietal epithelium of Bowman's capsule being cubical with occasional adhesions. Majority of glomeruli are normal. Tubules show marked swelling of epithelium due to parenchymatous degeneration. Few small foci of interstitial round-cell infiltration. No abnormality in vessels.

1929: Full-term pregnancy with no œdema at any time. Urine always contained albumin 1-2 parts per 1,000. Blood pressure at term was 160/100 mm.Hg settling to 105/75 two weeks after delivery.

1931: Full-term pregnancy. There was no œdema and only a trace of albumin in the urine. Blood pressure was 115/90. Six months after delivery, the patient had a puffy face and swollen legs lasting for one month. Albuminuria up to 10 parts per 1,000.

1932: Third pregnancy terminated by hysterotomy with sterilization. Blood pressure 125/80. Moderate albuminuria. Six weeks after operation, generalized œdema for eight weeks, with albuminuria up to 5 parts per 1,000.

1932–52: Well except for slight headaches and backache. Occasional slight ankle swelling in the evenings. Blood pressure readings varied from 150/110 to 110/70. Albumin present in all specimens tested except on one occasion in 1948. Renal function and intravenous pyelograms normal.

December 1952: No symptoms. Plasma albumin 3·9 grammes/100 ml., plasma globulin 2·3 grammes/100 ml.

January 1953: Generalized œdema with ascites and pleural effusions. Blood pressure 110/70 mm.Hg. Albuminuria up to 16 parts per 1,000. Blood urea 24 mg./100 ml. Urea clearance 83% and 65% of normal. Plasma cholesterol 710 mg./100 ml. Plasma albumin 1·8 grammes/100 ml., plasma globulin 2 grammes/100 ml. No diuresis occurred with three weeks' bed rest and low salt diet (daily sodium intake of 15 mEq.).

Treatment with cation exchange resin resulted in a loss of 13 kg. in body-weight, and 11 litres of water over twenty-one days. There was coincident decrease in the albuminuria from 25 grammes per day to 1·5 grammes per day. The serum albumin later rose to 2·1 grammes per litre, the patient becoming free of œdema.

Comment.—This patient was shown because of the length of history, the recurrence of anasarca after thirty years, and the two successful pregnancies. It is interesting to note that the blood pressure and the renal function are both still normal.

POSTSCRIPT.—August 1953: The patient is still free of œdema. There is no albuminuria and the plasma albumin is 4·8 grammes/100 ml.—H. G. L. L.-T.

[*May* 8, 1953]

MEETING HELD AT HORTON HOSPITAL, EPSOM

General Paralysis of the Insane (Two Cases).—M. WHELEN, M.D.

I.—S. F., female, aged 48. Admitted to Horton Hospital on 27.4.53 without any history.

On examination.—Childish, simple and confused. Memory impaired and only partially orientated. Face expressionless and silly. Tremor of tongue. Speech slow, hesitant and slurred. Slight tremor of fingers. Knee and ankle jerks exaggerated and equal.

Investigation.—Blood: W.R. negative; M.K.R. positive. C.S.F.: W.R. + 24; cells 0 per c.mm.; protein 65 mg.%. Lange 5555443210.

II.—B. S., male, aged 51. Admitted to Horton Hospital 10.11.52.

History.—Deterioration in personality since July 1952. September 1952: Became self-neglectful and flouted social and personal decencies. 6.10.52: Admitted to Maudsley Hospital, garrulous, euphoric and fantastically grandiose. Pupils unequal. Blood: W.R. positive. C.S.F.: W.R. + + +; cells 83 per c.mm.; protein 200 mg.%. Lange 4555321000. Given penicillin 300,000 units intramuscularly b.d., total 12·6 mega units. Became increasingly restive with aggressive outbursts and was finally transferred to the Observation Ward, certified and sent to Horton Hospital.

On examination.—Fantastically grandiose, garrulous and liable to aggressive outbursts. Pupils R. > L.

Investigation.—Blood: W.R. + 600; M.K.R. positive; Kahn 40 units. C.S.F.: W.R. + 48 +; cells 1 per c.mm.; protein 170 mg.%. Lange 5554321000.

Treatment.—January 1953: Malaria.

Progress.—As fantastically grandiose as ever but is better behaved and no longer aggressive; general condition shows a fair degree of improvement.

Comment.—These two cases were shown as illustrating the two main clinical types of G.P.I.—the simple dementing and the classical grandiose. The latter is now relatively rare, the former being the most usual form seen to-day.

Korsakoff's Psychosis (Three Cases).—G. H. A. CHAMBERLAIN, M.D.

I.—Female aged 61. Chronic alcoholic.

On admission (September 1952).—*Physically*: Smooth tongue; tachycardia, with a moderate degree of cardiac enlargement; peripheral neuritis—absent tendon-jerks with blunting of superficial sensibility. W.R. negative. *Mentally*: Confused, disorientated, mis-identifying those around her. A marked memory defect was present, particularly for recent occurrences and for names generally. Confabulation was a striking feature. Her mood was labile, ranging from euphoria to extreme agitation. She was visually hallucinated seeing "chinchilla mice" all over the ward.

Treatment.—100 mg. Benerva intramuscularly with vitamin B-complex tablets, 2 t.d.s., for a month, followed by vitamin B tablets up to April 1953.

Progress.—The confusion, visual hallucinations and the agitation rapidly subsided. After two months her deep reflexes were reappearing, but the memory defect was still prominent.

Present condition.—The peripheral neuritis has responded completely. Her power of immediate recall is so good that she can carry out a complicated day's shopping without needing a written list; but her memory is still patchy, and she covers up this weakness by fabricatures.

Comment.—Of interest were the initial features suggestive of delirium tremens (e.g. the characteristic hallucinations). As is customary, her physical signs have cleared up more rapidly and completely than the mental symptoms. This case has shown a relatively good response to treatment.

II.—Female aged 57. History of heavy drinking for some years.

On admission (January 1952).—*Physically:* Hypertensive (blood pressure 200/120), with cardiac enlargement and œdema of the ankles. Severe degree of peripheral neuritis was present—absent tendon-jerks, loss of superficial sensibility, extreme tenderness of the limbs on pressure, marked muscular wasting and loss of power, ataxia. W.R. negative.

Mentally: She was confused, disorientated and confabulating freely; e.g. she said she was in Nova Scotia, supporting this statement by innumerable "details". A marked memory defect was present and she was doubly incontinent.

Treatment.—Aneurin HCl, 100 mg., and nicotinamide, 100 mg., daily by intramuscular injection for six months followed by vitamin B-complex tablets up to the present time. Physiotherapy was given for the first six months.

Progress.—She remained completely bedridden for over a month, the return of power in her limbs was very gradual, and she was still showing residual neurological signs up to the beginning of 1953 (i.e. for twelve months) since when they have disappeared.

Present condition.—She has regained full power in her limbs. She has some slight impairment of memory for recent events, but has ceased to confabulate.

Comments.—In this case the peripheral neuritis was the outstanding feature, and the physical and psychiatric responses to treatment have been satisfactory.

III.—Female, aged 76. History of long addiction to cheap "wines".

On admission (May 1951).—*Physically:* Cardiac enlargement present, with systolic apical murmur. Blood pressure 170/105. Tender hepatic enlargement. Severe peripheral neuritis with pupils reacting sluggishly to light. W.R. negative. *Mentally:* Disorientated with very gross memory defect. Confabulations of a fatuous and grandiose nature dominated all her conversation.

Treatment.—Aneurin (40 mg. intramuscularly and 60 mg. orally each day for three months) produced little effect upon her psychiatric syndrome or on the peripheral neuritis, but produced a rapid improvement of her cardiovascular symptoms. She has gradually deteriorated over the past two years.

Present condition.—She is very ataxic and her tendon-jerks can be elicited by reinforcement only. She is extremely demented. Immediate recall is so bad that she believes she has been in hospital for only twelve minutes. She continues to confabulate in a euphoric manner.

Comment.—The poor result here has been due, no doubt, in part, to senile changes.

Idiopathic Familial Methæmoglobinæmia (Two Cases).—W. W. KAY, M.Sc., M.B., F.R.I.C., and J. F. MACMAHON, M.D., D.P.M.

Siblings, aged 12 and 13, suffering from idiopathic familial methæmoglobinæmia were presented to the meeting.

A younger sister is also the subject of this disorder but the remaining sibling and the parents are not affected. As these are the only cases of idiopathic familial methæmoglobinæmia known also to exhibit severe mental defect and marked areflexia, the association of nervous and mental abnormalities with this rare blood condition cannot (in the light of the evidence so far available) be regarded as statistically significant of a unitary pathology.

Gibson (1948) showed that familial methæmoglobinæmia was due to a deficiency of diaphorase I, a flavo-protein found normally in tissues. The disease therefore belongs to the group of inborn errors of metabolism.

Methæmoglobin, present normally in low concentration in red blood cells, is converted to hæmoglobin by an enzyme system of the pattern:

substrate + enzyme + co-enzyme⟶end-product.

The co-enzyme required is diaphorase I, deficiency of which allows methæmoglobin to accumulate in the red cells. A second enzyme system, in which a related but different co-enzyme—diaphorase II—takes part, can convert methæmoglobin to hæmoglobin if methylene-blue is also present. The administration of methylene-blue is one effective method of relieving the cyanosis of methæmoglobinæmics. Alternatively, there can be given large doses of ascorbic acid which, in high concentration in the blood, converts methæmoglobin to hæmoglobin, apparently by a direct reducing action.

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Myxœdema Associated with Paranoid States Treated with Thyroid Extract.—HENRY R. ROLLIN, M.D.

I. M. W., female, aged 52. Housekeeper.

Family history.—Revealed little significant material except that the father, who died of cancer in 1933, was described as an unpleasant person who had "all the vices".

Previous personality.—Patient is described by her sister as having always been hypersensitive with feelings of inferiority and often bad tempered.

Previous illness.—When 21 years of age she was treated in Australia with thyroid. The reason for this is not clear, but the treatment was abandoned after a period and she had had no further thyroid medication for many years prior to 1951.

History of present illness.—Whilst on holiday with her sister in Spain in 1950 a train they were travelling in was involved in a minor accident. Some suitcases were dislodged from the luggage rack which struck the patient on the head. That same afternoon her manner became strange: she was convinced she was being followed. Later she believed she was being pursued by income tax officials and that she would be gaoled. Her paranoid delusions became more widespread and aural hallucinations, also of a paranoid nature, appeared.

December 1951: She presented a typical picture of myxœdema. Thus, she was considerably overweight, her skin had a yellow parchment-like quality, her hair was thin and lustreless. She appeared dull and anergic; she talked openly of her delusions and hallucinations with, however, little emotion.

Treatment and progress.—The patient was given initially tab. thyroid grain ½ q.d.s. and the dose increased to grain 1 t.d.s. There was a rapid response from the physical standpoint: she began to lose weight (she has lost about 35 lb. since the onset of treatment), her skin lost its unhealthy colour, her hair became thick and regained its lustre. The improvement in her mental symptoms was slower but nevertheless definite. She became more active and interested in life. From time to time hallucinations have recurred, but she has been quite free from these now for some months.

Dr. R. A. J. Asher: This patient appears to have been a typical case of psychosis due to myxœdema. The response to thyroid in loss of weight, growth of hair and general well-being, leaves no room for doubt of the diagnosis of myxœdema. The type of psychosis with paranoid traits was that quite often seen in hypothyroidism and its improvement when thyroid treatment was given suggests strongly that the mental illness was due to the endocrine disease.

This condition is not rare; I reported 14 cases in 1949 and have seen others since. The diagnosis is made on the myxœdematous appearance of the patient and not on the kind of mental symptoms, because there is no specific mental state associated with hypothyroidism. It was fully described in 1888 by a special myxœdema committee of the Clinical Society of London. They said "delusions and hallucinations occur in nearly half the cases mainly where the disease is advanced". Advanced cases must have been common then because thyroid treatment was not known. Another description of hypothyroid psychosis occurs in Dr. A. J. Cronin's novel "The Citadel".

It is interesting that Dr. Rollin's patient was given thyroid for six months thirty years ago but it seems improbable that this fact is related to her recent illness.

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Section of Neurology

President—MACDONALD CRITCHLEY, M.D., F.R.C.P.

[*March* 5, 1953]

DISCUSSION ON THE DIFFERENTIAL DIAGNOSIS OF LESIONS OF THE POSTERIOR FOSSA

Professor Sir Geoffrey Jefferson: The prediction of the probable nature of the posterior fossa lesion is one of practical importance for the surgeon since he varies his approach to meet the individual kind of lesion. Diagnostic speculation on probability has therefore a special cogency. Often enough the histological type is known with certainty, as in the case of most, if not quite all, of the cerebello-pontine angle lesions, of the ependymomas—when the origin of the tumour from the floor of the fourth ventricle has been made clear by air or Myodil ventriculograms—or again in the case of some of the angiomas which may have been clearly depicted by vertebral angiography and, lastly, when evidence of malignancy elsewhere is to hand. But after deduction of such cases it is plain from the figures of the totals of my series that this still leaves the major proportion of posterior fossa tumours to be distinguished from one another. We should be greatly helped if we could point to certain leading characteristics proper to cerebellar lesions of different histological structures and gross form. To some extent we can do this though not always with certainty; not, be it said at once, with such confidence as to be able to formulate a syndrome for each tumour type. The generalization could indeed be made that it is more difficult to be as sure of the nature of a tumour in the posterior fossa than it is with the generality of hemispheral lesions.

It cannot be assumed that there is no problem at all in knowing whether a patient with clear evidence of tumour has a lesion above or below the tentorium. The old neurological dilemma, difficulty in discriminating between an ataxia and uncertainty of gait and limb movement of cerebral origin, or on the contrary of cerebellar, will be with us always. But this problem is no longer as serious in its possible consequences for the patient as it used to be. The uses of ventriculography and angiography in distinguishing between the sites of the lesions are well known; fractional ventriculography with Myodil has a special virtue in this respect. Furthermore, electro-encephalography is a great help since the cerebellar lesion is often characterized by rhythmical but quite symmetrical outbursts of frontal activity, a feature very uncommon when one or other frontal lobe is the primary seat of the lesion. A potent cause of uncertainty in my experience has shown itself when a tumour has not only involved the cerebellum but has crept down the restiform body into the posterior columnar nuclei, combining a sensory disturbance with cerebellar signs. In one such case a negative exploration of the parietal lobe was made before the real cause was discovered. It was a cerebellar hæmangioma with the distribution mentioned. There have been four or five similar clinical cases as a reminder that cerebellar lesions can and often do invade the peduncles (Thiébaut, 1948). Mistakes of one kind or another have led to wrong localization in only 5 of 635 cases, but there would have been more had it not been for the ancillary methods of diagnosis used.

Frequency and Age Incidence of Posterior Fossa Tumours

Table I is an analysis of the 635 histologically verified cases of the Manchester series to the end of 1951.

TABLE I

Astrocytomas	120	Acoustic neuromas	175
Medulloblastomas	84	Tuberculomas	26
Hæmangioblastomas	74	Secondary carcinomas	32
Ependymoblastomas	25	Various gliomas	26
Menjngiomas	29	Abscesses	36
Epidermoids	8		635

It is immediately apparent that the acoustic neuroma is the commonest tumour in the posterior fossa, in fact, above the age of 30 much the commonest. Another tumour high in frequency is the angioblastoma. It is met with at any age, my youngest case was in an infant a few months old. It runs through the decades at about the same level until its frequency falls in common with

all the gliomas in the fifth decade. In fact during the fifth decade and above, the acoustic neuroma has become truly dominant. The age incidence of the tumours has been figured in the accompanying histogram (Fig. 1) from which the shapes of the curves of age incidence can be clearly seen. They are not to be interpreted as meaning that the different types cannot occur at other ages. For example, there does not happen to be a medulloblastoma over 39, and although Cushing's (1930) oldest patient was 38, Spitz *et al.* (1947) reported 2 in their fifties.

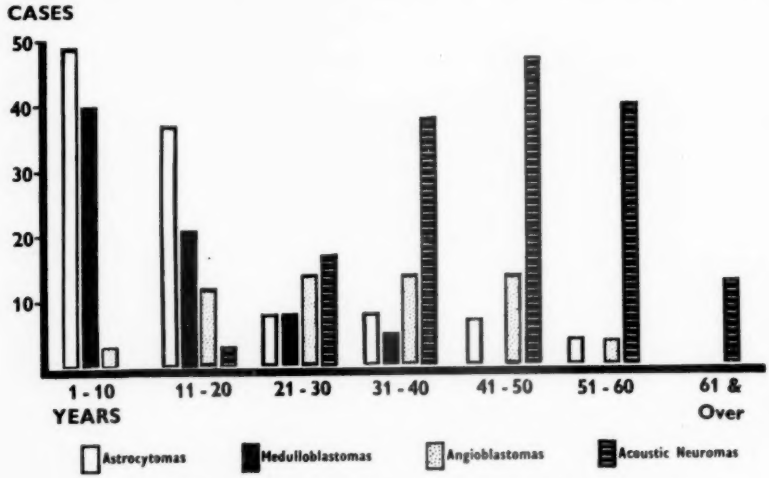

FIG. 1.—Age incidence of four tumour types in the posterior fossa.

The secondary carcinomas have not been included in this diagram. They would have shown, as one would expect, a rising incidence with age; most of the subjects were over 40 although secondary deposits occasionally occur in the very young. However, a man or woman in the fourth decade is still twice as likely to have a glioma as a secondary, in the fifth decade the odds are more evenly balanced. In the sixth decade if the patient does not have an acoustic neuroma he is very likely to have a carcinomatous cerebellar deposit though he could just possibly have a hæmangioma. The meningiomas, difficult tumours to diagnose except in the cerebello-pontine angle, are other possibles at any age above 20. Mr. Richard Johnson will comment on the Manchester examples of this tumour.

As is well known, the commonest tumours of youth, especially extreme youth, are the astrocytomas and medulloblastomas. In the first six years of life these were the dominant lesions in my series without a significant preponderance of one over the other (astrocytomas 25, medullobastomas 20). If the child is a male he is more likely to have a medulloblastoma. Up to and including age 15, 45 of my cases were males and 17 females, which agrees roughly with Cushing's proportion of 3 to 1. But Swan (1944) found that of 168 medulloblastomas collected from the literature 101 were in males and 54 in females, a 2 to 1 distribution. In the 56 cases of Ingraham, Bailey and Barker (1948) the incidence was about even between the sexes.

After this age and especially after ten years there is a slightly greater chance of the tumour being an astrocytoma because overall it is the commoner of the two tumours in the proportion of 3 to 2. Both types show a steep fall after the age of 20 but both may occur at any age. Spitz, Shenkin and Grant (1947) drew attention to the occurrence of medulloblastomas in the older age groups, pointing out that they then were likely to be tumours of the cerebellar lobes rather than of the vermis, their common site in infancy. My experience supports theirs. Furthermore, Ingraham, Bailey and Barker (1948) demonstrated that even in youth medulloblastomas arise in the cerebellar hemispheres (5 of 56 cases) or in the pons or cerebello-pontine angle (10 of 56 cases). A pontine tumour in a child instead of being the tuberculoma that it so often seemed to be fifty years ago may very well be a medulloblastoma. I have seen several but they were rarely verified since the patients were clearly inoperable and died at home.

These conclusions about the age incidence of posterior fossa lesions is important because, in reaching a diagnosis, due weight must be given to age in conjunction with the history and clinical signs. In this respect an analysis of a large series like this has its value. When my experience was smaller I could not have been so sure of the dominance of the acoustic

neuromas, for example, or of the wide and rather even age spread of the angioblastomas. The preponderance of the acoustic neuromas was plain from Cushing's cases (1932) but he might have had an undue proportion of them just as he had of pituitary adenomas. He had on the contrary no more than some 31 angioblastomas. Olivecrona (1952), on the other hand, had 70 and again his 349 acoustic neuromas dominate the posterior fossa lesion. Hesitation in agreeing about the position of the VIII nerve tumours in the scale of incidence comes from the fact that the gliomas and angiomas together certainly outweigh the neuromas. We think of patients with cerebellar tumours as young people and naturally and properly think of them as glioma subjects.

We must now turn to the neurological differentiation of posterior fossa tumours.

Differentiation on Neurological Evidence

The classical signs of cerebellar decomposition of movement in man, described originally by Grainger Stewart and Gordon Holmes in 1904 and elaborated in greater and greater detail by Holmes subsequently in studies which culminated in his classical paper "The Cerebellum of Man" in 1939, are far from common if they are expected in textbook form. From signs alone it is indeed not always possible to be sure on which side a tumour lies unless it occupies a cerebello-pontine angle. That was made clear by a preliminary survey of my cerebellar tumours by Schorstein in 1938. The reason is that most cerebellar gliomas are not in the lateral lobes but in or near the mid-line, hence are ambivalent. "Mid-line" is, to be sure, no better than a relative term as a description of a cerebellar tumour since close limitation to the vermis alone is practically impossible except for a very small tumour, so narrow is this structure. The medulloblastomas, which come closest to the strict anatomical description of vermis tumour, have commonly reached such dimensions by the time that they come under observation that they have invaded the lateral lobes to some extent and, not uncommonly, the insertion of the roof of the fourth ventricle into its floor. The mid-line astrocytomas start either in the vermis or in the medial third of a cerebellar lobe close by whence they grow equally into their proper lobe and into the vermis and indeed often across it into the opposite lobe, either as solid or cystic extension. Even the fourth ventricle ependymoblastomas which are certainly mid-line structures may proliferate into the lateral recess of that ventricle. Ependymal tissue very occasionally produces a cyst in the lateral cerebello-pontine angle (Jefferson and Hardman, 1938) though that is beside the present point. The commonest distribution of the cerebellar gliomas has been put in diagrammatic form in Fig. 2. For reasons already given the figure is no more than an approximation. A tumour as seen at operation may be larger than it appears whilst, as for assessing its functional effect, if it is benign, it may compress and push aside cerebellar tissue without seriously impairing its activity. This certainly is true of the astrocytomas and most of the angioblastomatous cysts of the neo-cerebellum. The key to the physiological problem set by the existence of decisive signs indicative of a lateral lobe tumour demonstrable to everybody's satisfaction and the discovery later of a mid-line tumour is to be found, I suggest, in the relation of the growth to the dentate nuclei and their outflows. These structures, the effective agents of the neo-cerebellum in particular, lie no more than 2 cm. or so lateral to the roof of the fourth ventricle and nearer at some points. One or the other is easily within reach of a vermis tumour; when one is damaged and the other spared unilateral disturbances of movement will result. The dentate outflows converging as they do on the mid-line are especially vulnerable in high vermis tumours.

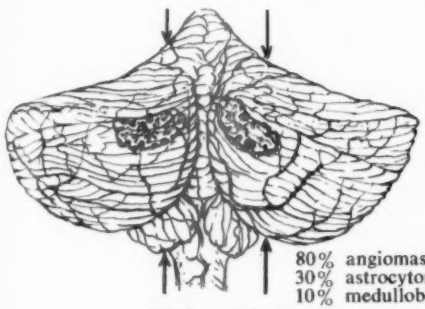

FIG. 2.—Dentate nuclei in relation to mid-line tumours of cerebellum.

Attention must be drawn to the fact that tumours do not notably invade or destroy the cerebellar cortex. In this respect they resemble the hemispheral gliomas, the chief effects of which are produced by disturbance of projection tracts and deep interneuronal connexions. In much the same way tumours cause cerebellar dysfunction by (*a*) interference with the dentate nuclei and perhaps even more generally by (*b*) compression or invasion of the cerebellar inputs and outputs through the peduncles. Neurologists have not hitherto paid sufficient attention to this fact, one that I shall return to again in relation to the acoustic neuroma; it is an important matter deserving further study.

Such factors make it very difficult to formulate a crisp picture of the difference between the signs produced by the four common groups of intrinsic tumour. From what has gone before and with reference to the histogram of age incidence (Fig. 1) and the diagram of sites of election (Fig. 2) it is clear that unilateral cerebellar signs are likely to be caused by an anatomically unilateral lesion much more often in persons over 20 than in the very young.

The vermis syndrome well, if briefly, described by Cushing (1930) but not named as such by him is characterized by unsteadiness in walking and as the tumour progresses withdrawal from anything but the most tentative of steps. Nystagmus was frequently absent or contestable. A thumbnail sketch of the cerebellar tumour in infancy would take this shape:

History six weeks to one year unexplained malaise, listlessness, fretfulness (often striking features), vomiting, headaches. Unsteadiness on feet one to five months. Cerebellar signs outspoken, more pronounced in the legs than in the arms and more evident still when the child stands, walks or turns. Cerebellar signs often more pronounced on one side though usually present in some degree on both. Reflex activity in the limbs normal, sometimes increased, or abolished in very ill high-pressure cases. Nystagmus may be absent but is present more often than absent. Head enlarged slightly, sutures spread on X-ray. Bulbo-spinal signs, shown by difficulty in starting micturition, dysphagia, indistinct speech and extensor plantar responses present rarely. These effects may be due to invasion of the medulla but are often caused by the prolongation of a tongue of tumour or a swollen cerebellar tonsil down to the second or even third cervical segment with the same effects as a high spinal tumour.

The history in the astrocytomas is sometimes longer, up to two years. Its length depends greatly on the degree of enlightenment of the child's medical attendant and on the speed of development of the lesion. Rapid cyst formation produces a very acute picture and a dangerous state especially in the angioblastomas requiring urgent surgery. The degree to which the fourth ventricle is dilated by many vermis tumours is remarkable. In its floor are the facial tubercles, anatomical features that suggest that the frequent presence of unilateral facial weakness and depressed corneal reflex may be due to unequal pressure on the ventricular floor. This is no more than a suggestion. On the other hand, it is quite certain that injuries to the facial tubercle produce a very interesting syndrome of palsy of the VI and VII nerves and paralysis of conjugate lateral movements of the eyes (as described by Jefferson and Johnson in a paper awaiting publication). Abducens weakness is more common, of course (unilateral 36, bilateral in another 13%), but is never an early sign and may be due sometimes to the pressure in the fourth ventricle though more often to extra-cerebral shifts and stresses.

It is a striking feature of the vermis tumour that disorganization of movement is more pronounced in the lower limbs and is more easily demonstrated by the patient walking than by testing him for dysmetria in bed. Until recently the study of cerebellar tumours has supported the original physiological observations of Flourens, Luciani and Sherrington that the cerebellum does not show any clear signs of discrete localization of limb, head or trunk control. The revision of cortical localization in the cerebellum brought about by Snider and Stowell (1944), Adrian (1943), Chang *et al.* (1947), Nulsen *et al.* (1949) indicates that sharply defined localization exists in the normal animal. In patients with cerebellar tumours there is every reason why functional disturbance should not be limited to one part of the body since tumours are too large in relation to the cerebellar mass. Yet I strongly suspect that more signs of localization are sometimes present than we realize. Thus a girl aged 14, an ardent hockey player, had first discovered her disability by frequent falling without dizziness on the playing field and an astrocytoma was found and removed high in the vermis extending to the lingula, i.e. it lay in the part more closely linked physiologically with the lower limbs and their inhibition. On the other hand head postures, tilts one way or another, are often adopted not because of cerebellar atonia but because tonsillar herniation makes a certain attitude more comfortable than any other. I am sure that they are more often due to disturbances of the labyrinthine components than to neo-cerebellar defects. In the main it can be said that destructive lesions of the vermis such as those caused by medulloblastomas cause more dilapidation of postural control than any other. But unhappily they are not clear physiological material since they are often made generally ill by the high compression of the brain-stem in the posterior fossa as well as by obstructive hydrocephalus.

Cerebrospinal fluid.—No sure conclusions can be drawn from the cerebrospinal fluid. Because of high pressure lumbar puncture is not often performed. After scrutiny of my records it is clear that only the hæmangiomas tend to run to high albumin counts—3 grammes, 600 m., 550 mg.%, and in one a yellow fluid. Recently 2 cases of subarachnoid hæmorrhage have been found to be due to unsuspected cerebellar angiomas. Curiously the medulloblastomas, chemically active tumours it would have been thought, do not as a rule run much above normal. Nor for that matter do the average hæmangiomas but a greatly raised level of albumin would suggest a tumour of that type or an acoustic neuroma (average between 200 and 300 mg.%). The contents of cerebellar cysts contain about the same amount of albumin as the adventitious arachnoidal cysts covering some acoustic neuromas, i.e. from 1·5 to 6% in my series.

Vertigo in Patients with Gliomas

Much interest was aroused amongst physiologists by the discovery of the so-called flocculo-nodular syndrome of vertigo of cerebellar origin, based on the work of Larsell (1937) and Dow (1938) and Botterell and Fulton (1938), and that leads at once to the interesting question of dizziness in patients with cerebellar tumours. Persistent enquiry is usually needed to find out what a patient means by dizziness. It is a subject that cannot be discussed with young children. Frequently it is used as a popular synonym for ataxia in walking, other times it is a description of a feeling of "swimminess" or light-headedness when they rise, often they have to pause for a few moments and hold on before walking away after rising from sitting or lying. That kind is probably of labyrinthine origin but it is gone in a few seconds. Another cause of dizziness is diplopia well shown when a cerebellar patient gives up riding a bicycle because the rapid succession of double images makes him feel insecure. In differentiating the true from the false vertigos attention must be directed particularly to the difference between dizziness on movement which is mainly cerebellar and dizziness at rest or change of head posture, a truly labyrinthine affair. But I am aware that the two overlap in some degree. We have, I feel sure, been too reluctant to concede that dizziness can be a real consequence of pure cerebellar lesions (*see* C. P. Symonds, 1952, on this subject). There are a few cases in which real vertigo scarcely, if at all, different from a labyrinthine vertiginous crisis is caused by a localized glioma. The following is such a case, studied and operated upon in my Unit, where he chanced to be working, by E. H. Botterell of Toronto, and diagnosed as true vertigo of palæo-cerebellar origin.

Case 1.—Severe vertiginous attacks. Discovery of a small ependymoma in region of flocculus and nodule. R. S., aged 32, No. 320/40, was admitted to the Manchester Royal Infirmary November 1940. Nine months previously he had had his first two attacks of vertigo "the floor came up and hit him and the room went round all ways"; the duration of the attacks was a few minutes during which time he had to lie on the floor. After this the attacks came more and more often until they were daily events. There was no doubt that there was a real feeling of rotation of objects in the vertical plane forwards commencing abruptly and incapacitating him for movement until it died away in a few minutes leaving him badly upset. He thought that the attacks were induced by sudden increases in his headache and sometimes he vomited in them. Examination showed papilloedema, ocular movements full in range, rapid nystagmus on fixation only to the extreme right and left. Tone in the limbs was not affected. The patient had noticed a disturbance of equilibrium as he walked and turned. Botterell wrote of this patient's performance that "We were completely unable to demonstrate errors of rate, range, direction or force of voluntary movement to account for the ataxia of gait and posture. He walked reasonably well without deviating to either side but tottered slightly after two or three rapid turns. He is excessively readily displaced by a gentle push, particularly is this so backwards. The signs suggest a lesion in the nodulo-floccular apparatus, the vestibular component, of the cerebellum". A small well-defined tumour, 2·0 cm. in diameter, later proved to be an ependymoma (Dr. E. Pollak) was then removed from the extreme lower end of the vermis in the roof of the fourth ventricle where it almost completely obstructed the foramen of Magendie (*see* Fig. 3, 1). The patient is well thirteen years later. The small size of this tumour makes this case one of considerable physiological importance.

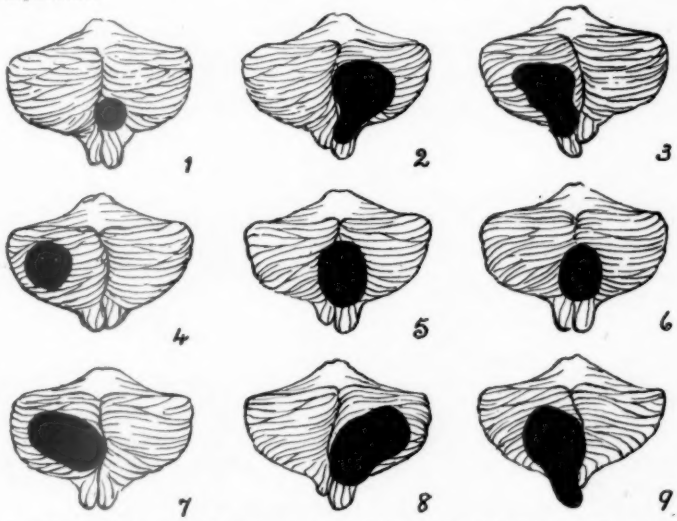

FIG. 3.—Sites of gliomas in the patients with vertigo described in the text, Cases I to IX.

In a random selection of 100 tumours, excluding acoustic neuromas and posterior fossa meningiomas, there were 20 cases who named dizziness as an important complaint. 11 of these were excluded as coming under the categories already mentioned, but I am not as sure as I should like to be that I have been right in rejecting all the 11. One of the accepted cases has just been described. The other 8 with attacks suspiciously like labyrinthine crises were as follows: the sites of their lesions have been illustrated diagrammatically in Fig. 3.

Case II.—D. C., aged 16. 11/43. A cystic astrocytoma in the right lobe of the cerebellum leading into the right tonsil. Highly compressed. For one year occasional sudden attacks of rotational dizziness, once frequent attacks for a period of five days. Was stone deaf in right ear but after operation the deafness disappeared gradually.

Case III.—M. N., aged 17. 211/37. Hæmangiomatous cyst in the left lobe and tonsil, nodule at junction of tonsil and vermis, eight months' history. Attacks in which objects rotate to left. These might come when the patient was lying in bed and were an early feature. Hearing normal.

Case IV.—T. B., aged 54. PPH/46. Secondary carcinoma in left lobe, sudden attacks of dizziness on moving her head, a violent whirl during which she dared not move.

Case V.—A. B., aged 12. 5/31. Medulloblastoma in lower vermis, three years' history of vertigo, headache and flushing. Had held head very still the last six months because movement precipitated dizziness and vomiting. He liked to be held, because he felt as if he was falling or going far down in a fast lift. Not deaf. Vertiginous attacks worse again past six months, started very abruptly, held tight whilst they lasted, usually induced by movement such as turning over in bed.

Case VI.—J. H., aged 33. 162/33. Ependymoblastoma arising in lower two-thirds of floor of fourth ventricle, dizziness seven months induced by sudden movements of head, falls to the ground because of it, quick recovery. Frequent. Both labyrinths failed to give reactions to caloric tests, slightly deaf in both ears. Vertigo was the first sign in this case of the tumour's presence. The explanation in this case was in all probability direct disturbance of the vestibular nuclei in the ventricle's floor laterally.

Case VII.—B. H., aged 46. 281/45. Left-sided hæmangiomatous cyst, sudden vertiginous attacks in which objects moved from left to right, frequent attacks of dizziness at rest.

Case VIII.—P. M., aged 43. 204/40. Astroblastoma right lobe and vermis. Two-year history of increasingly severe headache. Six weeks' history of dizziness coming in attacks in which he would stagger, duration a minute or two.

Case IX.—A. C., aged 52. 215376/51. Angiomatous cyst left lobe and tonsil; five months' history sudden attacks vertigo and headache, least effort brought on dizziness, vertigo on bending down, objects rotate rapidly and disconcertingly, brief duration, fall to left in the attacks. No deafness. Bilateral abducens palsy and left facial paresis.

It will be observed that in 7 out of these 9 cases the tonsil or lower vermis or ventricular floor was involved. One only was temporarily deaf in one ear from an unknown cause, one was slightly deaf in both ears but was reported by the otologists as having inactive labyrinths on both sides. The labyrinthine reactions of the remainder were not tested. It would be going too far to suggest that the examples reported above are proof positive that a patient with a tonsillar or low vermis lesion will necessarily have vertigo. I know that it is not so, for others with tumours in similar locations have not had sudden crises of imbalance. But one cannot be sure that in those that did have those attacks there was not some small difference in the amount of injury produced by the tumours to the flocculus or nodule, or their connexions with the vestibular nuclei. And it is the fact that, given a tumour high in the vermis or well away from the mid-line, vertigo occurred only in 1 of 100 cases (Case IV). That is a very different story from the acoustic neuromas of whom 40% had vertigo; a higher figure than I should have given some years ago.

The Acoustic Neuromas and Cerebello-pontine Lesions

These would range from the acoustic neuroma to the meningioma, angioma, epidermoid, and aneurysm but I shall confine myself to the first.

The symptoms and clinical signs produced by the acoustic neuromas, characteristic also in large degree of other lesions in the cerebello-pontine angle, are amongst the best known of neurological syndromes. They are recapitulated now only to introduce brief comment; monaural deafness (complete or partial), headache, unsteadiness in gait, dead labyrinth, depression of the ipsilateral corneal reflex, ipsilateral cerebellar signs sometimes associated with enhancement of the contralateral limb reflexes, trigeminal hypo-æsthesia or pain, X-ray evidence of enlargement of the porus internus or posterior petrous erosion, rise in C.S.F. protein, usually above 100 and less than 300 mg.%. Ventriculography should demonstrate torsion of the ventricular floor (Twining, 1939) or a filling defect but it is not often needed.

The work of Hallpike and his collaborators has done much to make the diagnosis of these tumours easier. Otological testing at the present time plays a dominant role in the differentiation of such cerebellar patients as are in a fit state or of an age to allow of accurate observation (Dix and Hallpike, 1952).

Unilateral deafness is the most famous of these signs and it is the one fundamental thing so frequently not recognized by the patients themselves as linked intimately with their complaints.

The troubles they experience are most often due to blockage of the C.S.F. pathways, to the tumour's indentation of the pons or cerebellum or to its pressure on neighbouring nerves. Patients do not understand these mechanisms and no man unversed in intracranial physiology could explain their sequence. How could a sufferer know that the tinglings that he feels in his face are related to his painless deaf ear? How often, for that matter, do persons with paroxysmal vertigo attribute it of their own unprompted accord to the same cause as their defective hearing?—rather more often, I should answer, than the neuroma patient attributes his troubles correctly to their source. Thus it is that individuals whose troubles are due to acoustic neuromas nearly always present at first as cerebellar tumours or even as plain severe high-grade intracranial pressure patients. As for the signs enumerated, their incidence and their importance vary greatly, many may be lacking—even the deafness, as in my most recent case in which hearing was excellent on the affected side, twice as good as on the other which had been mildly infected. When it is present it is only mentioned by some 25% of the patients spontaneously, the symptom has to be asked for in the others and the occasional person has not realized that he is deaf or how deaf he is until tested. The symptoms in order of their onset as given by my subjects were headache, unsteadiness of the feet, vomiting, numbness of the face, vertiginous attacks, deafness. All of these patients (there are exceptions but they are rare) have nystagmus; it is fast to the opposite, coarse and sustained towards the same side when the tumour is of any size. This is unlike the cerebellar gliomas where nystagmus was absent in 20 of a 100 cases, and was classically coarse, sustained and awakened by deviations of not more than 45 degrees from the mid-point in only 30. It was most often present in destructive lesions of one lobe and in tumours of the lower vermis. Nystagmus is certainly more common in recess tumours than in those of intra-cerebellar origin. The deduction must be that the recess tumour is better situated to disturb labyrinthine, and in many ways, cerebellar function than its intrinsic fellow. This leads me to make the only other point that concerns me on this occasion (a full description of my acoustic neuroma series is to appear elsewhere in the future; the Queen Square cases were submitted to an admirable review by Edwards and Paterson, 1952). The matter to which I want to draw attention is the anatomical relation of the acoustic neuroma to the cerebellum. Although the large cysts that some have behind them press the cerebellum aside, the tumours themselves have little to do with the cerebellar folia but are in intimate relation to the brain-stem and ponto-medullary junction. As they develop they seem to grow more and more upwards and medially to indent the middle cerebellar peduncle, the brachium pontis, and extend upwards to the side of the caudal end of the mid-brain and on to the front of the pons as far as the basilar artery. As a result there ensues compression of the middle cerebellar peduncle and it seems to me most probable that the cerebellar signs of acoustic neuroma are mainly due to interference with conduction in this structure. Such experimental evidence as there is (e.g. Botterell and Fulton, 1938) shows that gross cerebellar deficit follows section of the middle peduncle but of all the cerebellar connexions it is the most difficult to divide cleanly. The deep indentation caused by a somewhat worse than average neuroma is shown in Fig. 4. Those tumours which indent it less are those in which cerebellar signs are fewest. An extension of the tumour medially produces pressure on the pyramidal tract above its decussation and consequently enhancement of contralateral reflexes with in some 20–25% of cases alterations in the plantar response. The effects on the labyrinthine nuclei need further consideration than I can give them. Trigeminal neuromas (7 cases) and lateral recess meningiomas often compress the caudal mid-brain more and the middle peduncle only a little less. They are more likely than the acoustics, if there are no general pressure signs, to be mistaken for disseminated sclerosis.

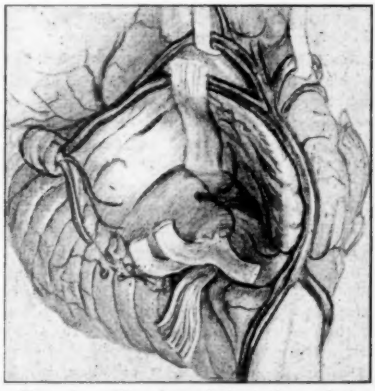

FIG. 4. — The deep indentation of the middle cerebellar peduncle caused by an acoustic neuroma.

Conclusion

This review makes it plain that in the differential diagnosis of posterior fossa lesions we have to be guided by broad general principles derived from diverse sources. It has been shown that no tumour except the commonest of them all, the acoustic neuroma, is specific to one invariable site. For the rest, the neurologist has to draw his conclusions as best he can, being guided by statistical probability. Decomposition of movement occurs with any destructive lesion of the cerebellum and all the intrinsic tumours may behave in that respect in much the same way—

the medulloblastomas by frank invasion, the angioblastomas by bleeding, the astrocytomas by rapid cyst formation. The clinician will be right more often than he is wrong in his differential diagnosis.

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Dr. J. Hamilton Paterson: I propose to confine my remarks to a brief consideration of some disorders involving the mid-brain, pons and medulla—in short, the brain-stem.

Encephalitis

The first condition, or rather group of conditions, I want to consider is that of encephalitis affecting the brain-stem in particular. The encephalitides are, of course, a hotchpotch of miscellaneous states which have a diverse ætiology and are acute or subacute in onset. Perhaps the term encephalopathy is more appropriate, as in only a few instances is the condition known to be caused by an infective agent, but encephalitis is a more euphonious term and its use has been hallowed by time. Usually when we make the diagnosis we are hardly able to qualify it in any useful way, so little would be gained by attempting any comprehensive clinical classification; suffice it to mention two types.

(1) Though the condition is now very rare, sporadic examples of an acute and apparently infective encephalitis which more or less closely resembles the classical picture of acute encephalitis lethargica are seen from time to time. Last year Barrett, Gairdner and McFarlan (1952) described a small outbreak in 8 children, 2 of whom died. The conspicuous clinical features were somnolence, extrapyramidal rigidity and tremor, with the addition of some pyramidal signs, but cranial nerve palsies of the kind which were frequently seen in Von Economo's encephalitis were only encountered in one child. The histological appearances were more akin to poliomyelitis than to the former condition, although their clinical state bore little resemblance to polio. After comparing their cases with other known forms of acute epidemic encephalitis of virus origin, they concluded that this outbreak was either one of poliomyelitis with most unusual features, or was due to some hitherto undescribed type of encephalitis.

(2) Two years ago, Bickerstaff and Cloake published three interesting examples of what they termed mesencephalitis and rhombencephalitis. Their patients showed drowsiness, oculomotor palsies, facial palsy and ataxia. Two had total bulbar paralysis in addition. The clinical course was that of gradual progression in a few weeks to an almost moribund state, although subsequently improvement was rapid and eventually a complete recovery was made. I have seen a very similar case. The picture is not that of any of the known encephalitides due to virus infection, nor is it like the acute disseminated encephalomyelitides which follow one of the common exanthematous fevers. One might be tempted to regard it as being an unusual form of disseminated sclerosis were it not that, as Bickerstaff and Cloake (1951) point out, the absence of pyramidal tract involvement and the predominance of lower motor neurone palsies make this diagnosis a somewhat unlikely one.

In regard to the differential diagnosis of brain-stem encephalitis when, as not infrequently happens, it presents with fever and neck stiffness, it will, of course, be essential to exclude tuberculous meningitis and other pyogenic infections, although it is rare for the latter to show anything much in the way of brain-stem signs at an early stage. To this end a careful examination of the cerebrospinal fluid is of prime importance. Papillœdema is rare, but when it is present ventriculographic studies may be required to help exclude a lesion obstructing the cerebrospinal fluid pathways. Wernicke's encephalopathy should also be considered in view

of the prominence of ocular palsies and nystagmus in this acute disorder. Apart from the fact that the cerebrospinal fluid, unlike that in most cases of acute encephalitis, is normal, a therapeutic trial of thiamine, given parenterally in large amounts, would probably soon settle the issue in cases of doubt, as the eye signs in Wernicke's state usually melt away rapidly with vitamin B_1. Other conditions of acute or subacute onset which give rise to multiple cranial nerve palsies include the acute neuropathies such as that due to porphyria, poliomyelitis and botulism, but these need only be mentioned, as usually attendant features make the diagnosis an easy matter.

Disseminated Sclerosis

In considering disseminated sclerosis, I find myself uneasily wondering how often I have erroneously made this diagnosis in patients whose symptoms are episodic and recurrent and suggest a brain-stem lesion. For, as will be seen, other conditions of an entirely different nature may mimic disseminated sclerosis very closely. Some of these are of obscure origin. A few years ago I watched 2 patients succumb to disorders which closely resembled disseminated sclerosis, but though the latter was definitely ruled out when their brains came to be examined, the nature of the condition in both cases still remains unidentified despite the most detailed histological studies.

One of the two was a young man of 33 who was admitted into the National Hospital under the care of Sir Charles Symonds. He gave a history of transient diplopia, dysarthria and weakness and numbness of the left leg two years previously, but after two months these symptoms cleared up completely. Thereafter he remained physically well up to three months before admission, although he had shown somewhat marked behaviour and personality changes. His final attack was characterized by diplopia, dysarthria, progressive ataxia and disturbances of micturition. On examination he showed marked ocular palsies and nystagmus, facial weakness, palatal paresis, cerebellar ataxia of all limbs and bilateral pyramidal signs. Routine investigations revealed little of note save for some 80 lymphocytes per c.mm. and a mild increase of protein in the cerebrospinal fluid. His condition steadily deteriorated and he died a month later with a profound bulbar palsy. Examination of his brain showed multiple areas of softening of varying age in the medulla, pons and internal capsules. Histology of the fresher lesions showed zones of microglial and astrocytic proliferation surrounding central regions loaded with polymorphs. The near-by vessel walls were heavily infiltrated with lymphocytes but myelin sheaths were everywhere intact save in the areas of softening.

There are instances of course in which, as there is no evidence of more than one lesion, and no history of recurring episodes, disseminated sclerosis as a clinical diagnosis can hardly be justified, although subsequent histological studies show this to be the case. These are fortunately rare. But it is not unlikely that even in "typical" cases an error in diagnosis is made more frequently than we would like to think.

Angiomas and Aneurysms

I would like to mention two of the vascular conditions which may involve the brain-stem, namely vascular anomalies of an angiomatous nature and aneurysms.

As regards posterior fossa angiomatous malformations it is convenient to distinguish between the large arteriovenous racemose type and the malformations of pre-capillary or capillary size which are often referred to as telangiectases. As yet relatively few of the former have been reported in the literature although now that vertebral angiography has become a comparatively simple routine procedure they are being found much more frequently. Their clinical effects are apparently of the same order as those produced by supra-tentorial angiomas; thus they may bleed into the subarachnoid space or by hæmorrhage and in other ways cause temporary or permanent interference with the function of the nervous structures which they surround or in which they lie embedded.

A patient of Dr. Denis Brinton (Hierons, 1953), shown to this Section on 6.11.52, was a woman of 26 who gave a history of recurrent facial pain for four years which, curiously enough, only troubled her during the summer months. She had also noticed transient numbness of her tongue and roof of the mouth, and once her vision had been blurred for two weeks. She denied headaches and diplopia but admitted that when younger she had often noticed a beating noise in her head. She had nystagmus, bilateral cerebellar signs, absent abdominal reflexes and a left extensor plantar response. It is not surprising, therefore, that she had been regarded as having disseminated sclerosis. However, listening to her skull gave the clue to the diagnosis, for a very loud bruit was audible in the right mastoid region. Two similarly instructive cases, one of whom had been regarded for years as having a slowly growing brain-stem glioma, have recently been mentioned by Sutton (1952) in a paper on vertebral angiography.

As often as not telangiectases of the pons and medulla are symptomless during life and are only incidentally found at post-mortem examinations. Occasionally, however, they may resemble disseminated sclerosis and other brain-stem conditions though few such cases have been described. Dr. Purdon Martin (1951) cited one, his clinical diagnosis being confirmed by

autopsy, and Elkington in 1935 reported the case of a woman of 27 whose symptoms and signs suggested a lateral recess tumour. She died two weeks after an exploratory operation and it was found that hæmorrhage had occurred from a telangiectatic malformation of the left half of the pons and left middle cerebellar peduncle. Others have described patients who have died rapidly from hæmorrhage from these malformations. They may present in another way, as Sir Charles Symonds (1948) has pointed out, namely in those rare instances in which quite severe brain-stem symptoms and signs rapidly develop after a comparatively trivial head injury. Bergman (1950) collected four confirmed examples from the literature in which the anomaly had undoubtedly caused symptoms and signs during life, and added one of his own. He was a boy who was thought to have a pontine tumour. 2 of the others he mentioned had progressive bulbar palsies and 1 had had recurrent subarachnoid hæmorrhages over many years. In 4 out of the 5 patients he cited, post-mortem examination revealed other angiomas elsewhere. A point of interest is that in several instances the small intra-pontine telangiectases were associated with much larger vascular tangles outside the brain-stem which would presumably have been demonstrable by vertebral angiography.

There appears to be more information available concerning aneurysms of the basilar and vertebral arteries and their branches. Some only betray their presence by bleeding, when either they are discovered on routine angiography or after the ensuing neurological signs have pointed to the posterior fossa as the site of the hæmorrhage. One woman I saw recently had been quite well prior to her subarachnoid hæmorrhage, but subsequently she developed signs of a cerebello-pontine angle lesion. Vertebral angiograms showed an aneurysm of the superior cerebellar artery on that side which Mr. Valentine Logue later removed very successfully, for she is now quite well. In other instances these aneurysms do not rupture, but by compression of near-by structures they may give rise to progressive signs which strongly suggest a tumour. I know of one patient in whom the pre-operative diagnosis of an acoustic tumour was supported by the clinical, radiological and otological findings, while even the cerebrospinal fluid showed an appropriately raised protein content. Fortunately at operation Mr. Wylie McKissock recognized it for what it was—a basilar aneurysm—and did nothing apart from taking scrapings from its wall to confirm his conclusions. In 1932 Strauss, Globus and Ginsburg described a basilar aneurysm in a boy of 17 which had caused numerous brain-stem signs including dysarthria and dysphagia. He had been thought to have encephalomyelitis. Others have described the compression effects of vertebral aneurysms and as Meadows (1951) pointed out they may simulate a tumour causing multiple unilateral cranial nerve palsies or a high cervical cord lesion. Clearly this is a field in which angiography can be very helpful.

Brain-stem Gliomas

I do not wish to say much about infiltrating gliomas of the brain-stem, but it is necessary to mention them as they may be difficult to diagnose, and they may mimic some of the conditions already discussed. As Guillain, Bertrand and Gruner (1945) remark in their monograph on these tumours, their onset is often rather acute and may be accompanied by a fever. Hence they may at this stage resemble an acute brain-stem encephalitis. They also quote others to the effect that these gliomas may be mistaken for acute disseminated sclerosis, for they do not often cause a raised intracranial pressure, and among the earliest troubles to develop are cerebellar and pyramidal disorders and lateral gaze palsies. Furthermore the course they take is often intermittent rather than one of steady progress. However, the radiologist can frequently demonstrate a significant displacement of the aqueduct and fourth ventricle and thus rule out an acute demyelinating disease.

Occasionally these tumours present in a very atypical way. Dr. Meadows had in his care a few years ago a small girl whose sole trouble for eighteen months was that she had a complete left III nerve palsy which had come on suddenly. As she also had bouts of pain above the left eye and in the left temple, it was thought that she might have an intracranial aneurysm. Only in the last two months of life did she develop more typical signs and symptoms. At autopsy a nodular mass of tumour tissue was seen to have grown out from the upper and anterior aspect of the pons to surround the left oculomotor nerve.

There are, of course, many other conditions which should be considered in the differential diagnosis of brain-stem lesions but my time is up. I am afraid that I have not been able to do justice even to the few conditions I have mentioned, but I have endeavoured to indicate some of the diagnostic difficulties they may present. However knowledgeable and skilful the neurologist may be in eliciting and interpreting physical signs, he will often be unable to arrive at the correct diagnosis of these conditions without the help of others; notably the neurosurgeon, otologist, pathologist and radiologist. These problems call for yet more team work. It is true that at present little can be done for most of these conditions, but surely this will not always be so. The day will probably come, for example, when we will be able to arrest the march of disseminated sclerosis. An accurate and, above all, early diagnosis of the malady will then be essential.

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Dr. J. W. D. Bull:

The Radiological Differential Diagnosis of Lesions of the Posterior Fossa

If radiology could provide all the help that might be expected of it ideally, it would be able to resolve two questions in every case presented as a possible posterior fossa tumour.

The first would be: "Is there a tumour in the posterior fossa or not?" and the second, "If there is a tumour present, what is its size, shape, position and pathological nature?"

I will try and deal with some aspects of these questions, and if time allows, touch on another closely related problem. This concerns the type of case which is sent to the radiologist as a posterior fossa tumour, but on radiological investigation proves to be a lesion elsewhere, often of the mid-brain. Such cases come within the realms of this discussion, for without careful radiology the posterior fossa may be unnecessarily opened.

With regard to the first question, by the time clinical symptoms develop we *nearly* always can demonstrate a posterior fossa tumour. The sylvian aqueduct and fourth ventricle are very sensitive indicators and in the very great majority of cases show some displacement or deformity after the advent of symptoms. It is at once apparent that one's faith in some form of contrast filling of the ventricular system for tumour localization is great.

But this faith is limited when one comes to answer the second question. Although the position of the tumour can usually be indicated fairly exactly, no accurate forecast of its size, shape or pathological nature is possible in very many cases. These limitations appear to be inherent in ventriculography in general, except in some of the relatively rare intraventricular tumours and a few others.

But the various methods of outlining the ventricular system—pneumo-ventriculography, positive contrast ventriculography and pneumo-encephalography—are only a part of neuroradiology and we must synthesize with them the other investigations of plain X-rays, tomography and angiography.

It might be hoped, indeed it was hoped, when percutaneous vertebral angiography became a practicable procedure four or five years ago, that it would provide the required additional information. Ventriculography would usually show where the tumour lay, but angiography might indicate its size, shape and pathology. However, Radner's monograph (1951) on 221 vertebral angiographies, which included 40 posterior fossa tumours, showed that angiography was infinitely less reliable than ventriculography in demonstrating the presence of a tumour, and in only 8 cases was the tumour outlined by its vessels (Table I). Our experiences have confirmed this. The dramatic picture obtained in one case is unfortunately very exceptional.

TABLE I.—RADNER (1951)—POSTERIOR FOSSA TUMOURS—VERTEBRAL ANGIOGRAPHY

	Number	Pathological vessels
Hemisphere		
Astrocytoma	4	0
Medulloblastomas	4	0
Hæmangioblastomas (Lindau)	5	4
Metastases	2	0
Abscesses	2	0
Fourth ventricle		
Ependymomas	2	0
Pons	2	0
Acoustic neuromas	10	2
Meningiomas	4	2
Giant-cell tumour occipital bone	1	0
Non-verified (shown by other radiographic methods)	4	0
Total	40	8

Case I.—The patient was a girl aged 17 who had been previously operated upon for a hæmangioblastoma. She developed signs of a recurrence and vertebral angiography clearly indicated the lesion (Figs. 1 and 2).

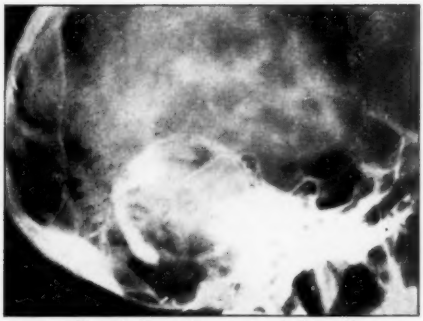


FIG. 1 (*Case I*).—Lateral view of hæmangioblastoma.

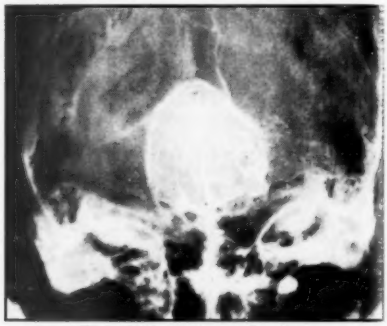


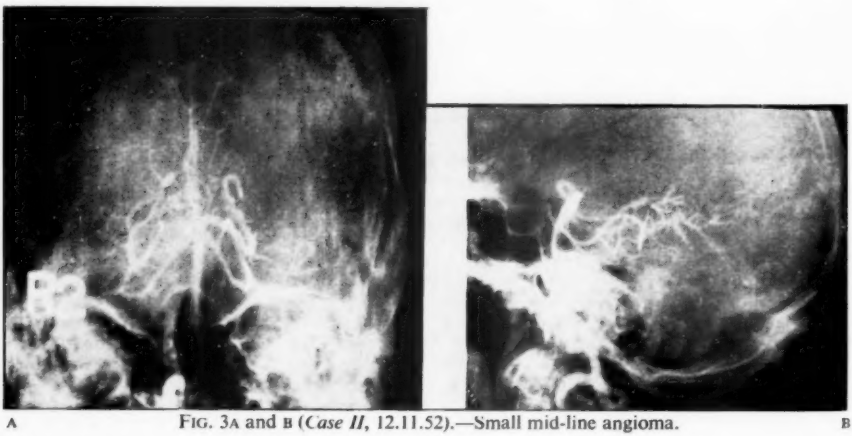
FIG. 2 (*Case I*).—A.P. view.

Recently Dr. Swithin Meadows had 2 sisters under his care, both with Lindau's disease in which he diagnosed cerebellar hæmangioblastomas. Mr. Wylie McKissock successfully removed a cerebellar hæmangioblastoma in each case. Vertebral angiography was performed in both cases, but in neither case could a definite tumour be seen. Subsequent ventriculography located the tumour in both the patients.

It is hardly surprising that angiography is so disappointing when one considers that the largest arteries supplying the posterior fossa structures are the anterior superior cerebellar pair. If one adds to this the petrous bones which superimpose themselves so densely, the picture is considerably obscured.

None the less angiography has a small, but limited, use in the posterior fossa, particularly in the diagnosis of aneurysms on the vertebral and basilar arteries and of posterior fossa angiomas, provided they are of sufficient size. The following case is an example.

Case II.—A woman aged 50 collapsed in the street. Subarachnoid hæmorrhage was suspected and was confirmed by lumbar puncture. Bilateral carotid angiography failed to reveal any source of hæmorrhage, so vertebral angiography was performed and revealed a small angioma in the mid-line apparently on or near the surface of the apex of the cerebellum (Fig. 3). Ventriculography showed a very small filling defect in the roof of the fourth ventricle which was thought to be caused by a small hæmatoma. There was no hydrocephalus (Fig. 4).



A FIG. 3A and B (*Case II*, 12.11.52).—Small mid-line angioma. B

Mr. V. Logue removed a small angioma and a blood clot the size of a walnut. Post-operative vertebral angiography showed a normal vascular pattern. The anterior superior cerebellar arteries were considerably smaller than at the first arteriogram (Fig. 5). Larger angiomas are proportionately more easily demonstrated.

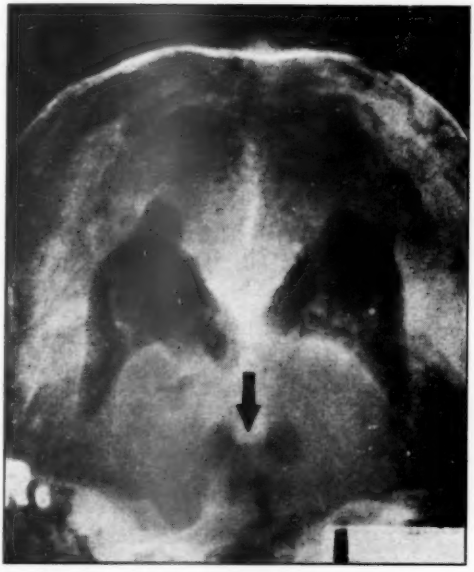
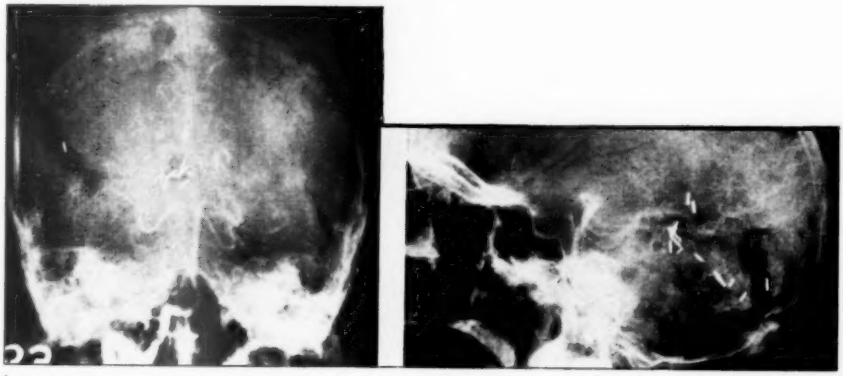


FIG. 4 (*Case II*, 27.11.52).—Ventriculogram showing defect in fourth ventricle (hæmatoma).



A B

FIG. 5A and B (*Case II*, 16.12.52).—Post-operative angiogram showing absence of pathological vessels in region of tantalum clips.

Plain X-rays

Let us now consider the value of plain X-rays. Here again the results are for the most part disappointing, but *never* should plain X-rays be omitted from the general preliminary examination. I must stress this because one has heard it said that the diagnosis of acoustic neuroma, for example, is sometimes so obvious clinically that plain X-rays are redundant. Such a teaching is most dangerous and sooner or later leads to an error in diagnosis. Other tumours even in the middle fossa, such as V nerve tumours, can simulate acoustic neuromas. Such a misdiagnosis will lead to a wrong surgical incision.

How then can plain X-rays help? They may show signs of pressure, as evidenced by sellar decalcification and later erosion, but the pressure may be produced by a lesion anywhere in the brain. Increase in the size of the posterior fossa is practically never observed. Very occasionally unilateral thinning and bulging of the infratentorial part of the squamous occipital bone is seen in the tumours of one cerebellar hemisphere. Calcification in posterior fossa tumours is exceedingly rare. Lysholm (1941) described calcification in 2 cases of meningioma of the cerebello-pontine angle, but these are very rare tumours and those few that I have seen have not been

calcified. Although it is said that large occipital emissary veins are seen in association with posterior fossa tumours, I have never been convinced of the value of this sign, and it certainly does not assist in differential diagnosis.

Dermoids growing from the region of the torcular are rare. Sometimes they cause a furrow in the bone. When this sign is present it is pathognomonic. Recently Logue and Till (1952) described the features of these tumours very clearly.

Apart from rarities there is only one tumour of the posterior fossa in which the plain X-rays are helpful in differential diagnosis—the acoustic neuroma. Since this tumour represents about one-third of all posterior fossa tumours, plain X-rays are important.

In the literature very widely varying opinions are given regarding their value in the diagnosis of VIII nerve tumours. Lassila (1937), one of Lysholm's assistants, described how 91% of 43 acoustic tumours confirmed by Olivecrona could be diagnosed on the plain X-rays. A recent monograph by Lundborg (1952) from the same hospital analysing 300 of Olivecrona's acoustic neuromas is more conservative. Lundborg states that plain X-rays were definitely positive in 63·2% of cases, and another 21·6%, he says, showed changes "which the roentgenologist believed worthy of notice, but which could not be considered clearly pathognomonic." The combined figure of certainties and suspicious cases in thus 84·8%. Recently I analysed the radiological findings of 50 confirmed acoustic neuromas and found that in 38 cases (76%) the internal auditory meatus was widened. Erosion of the petrous apex was detectable in 12 of these cases, but there was never erosion of the apex when the meatus was intact.

Plain X-rays will *never* be able to give the key to the diagnosis of all acoustic tumours for some are so centrally situated that they do not erode the meatus and a few others are too small to widen the meatus.

In examining the meatus and apex it is most important to take multiple projections. We always take half axial (Towne), full axial, per-orbital and Lysholm's modification of Stenvers' projection. The widening of the meatus is sometimes seen on one only of the projections.

These projections are also very useful in the differential diagnosis of lesions of the petrous apex. Such lesions are rare and many are extradural, and so perhaps more in the sphere of the neuro-otologist or radiotherapist than of the neurosurgeon.

Tomography

This procedure has not been found helpful in demonstrating posterior fossa lesions, except perhaps in indicating basilar impression more clearly.

Pneumoencephalography and Positive Contrast Ventriculography

Since most cases of posterior fossa tumour present with signs of pressure we usually employ ventriculography, though I personally feel that *controlled* encephalography should be used rather more. This method is even more necessary for the filling of the aqueduct and fourth ventricle with air when hydrocephalus is absent.

One has heard it stated by some experienced in this field that hydrocephalus is necessary for the diagnosis of posterior fossa tumours. This is not true. Furthermore, hydrocephalus is not necessarily indicative of a posterior fossa tumour. The tumour may lie anywhere from the foramen of Monro downwards. There are, of course, other causes of hydrocephalus besides tumour.

As illustrative examples one may quote the 50 cases of acoustic tumour already mentioned. Hydrocephalus was present in only 27 (54%). If the meatus is normal and hydrocephalus is absent the diagnosis may be very difficult and sometimes impossible radiologically. Often the only sign is rotation of the fourth ventricle. I have described this sign more fully elsewhere (1950).

We have no experience of pneumography of the cerebello-pontine angle cisterns in such tumours, a technique elaborated by Robertson (1946) of Melbourne and since then by Lindgren (1950) of Stockholm.

As already mentioned, the aqueduct and fourth ventricle are very sensitive structures and are displaced by nearly all posterior fossa tumours. For example, tumours of the hemispheres kink the aqueduct forwards and displace it and the fourth ventricle laterally. Superior vermis tumours kink the aqueduct forwards, but do not displace it or the aqueduct laterally. There is not time to discuss all the classical deformities produced by tumours in various sites.

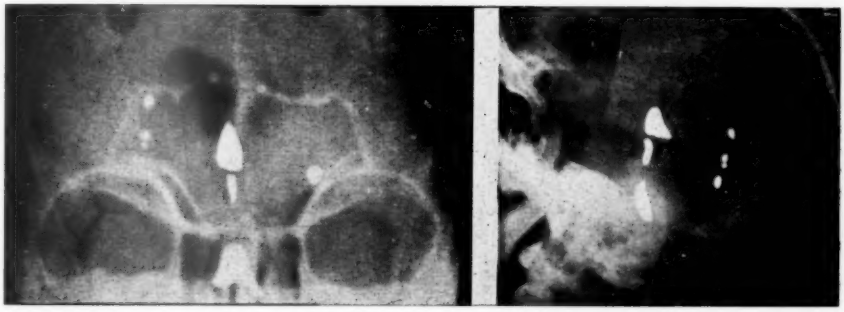
I would like to refute the common notion that posterior fossa tumours obstruct the aqueduct. Such a happening is very, very rare. If it were the rule, one could seldom localize posterior fossa tumours radiologically. The various deformities of the aqueduct and fourth ventricle produced by posterior fossa tumours were worked out very beautifully nearly two decades ago independently by Lysholm (1935) of Stockholm and Twining (1939) of Manchester. Their findings have shown us, in my opinion, that in general it is easier to localize infratentorial tumours than those lying supratentorially. One must remember that the aqueduct and fourth ventricle are there to be filled with air, difficult though it may sometimes be, and it can require two or even three attempts at manipulation before success is achieved.

Accurate localization for the surgeon is very important. This applies particularly to tumours *not* in the mid-line. In such cases only a unilateral incision need be made, thus shortening the operation and causing less trauma (Bull, 1953). Furthermore the surgeon can approach the tumour immediately without searching. This factor may save much operating time.

Tumours of the posterior fossa without hydrocephalus can be very difficult to demonstrate. Pontine tumours seldom show hydrocephalus, many in the angle do not, but those lying behind the axis of the aqueduct and fourth ventricle usually do.

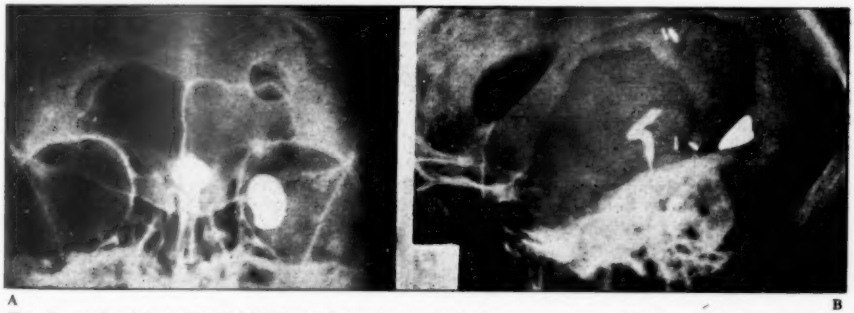
Case III.—A girl aged 10 (A. K.), with only a month's history suggesting a left cerebellar tumour, had a normal-sized ventricular system with no displacement of the aqueduct or fourth ventricle. Her condition deteriorated and we repeated the air studies a fortnight later by which time a considerable hydrocephalus had developed and a left cerebellar tumour was easily shown. It was an ependymoma.

Case IV.—An even more difficult case was a man aged 32 (E. H.) who, briefly, had a four-week history of headache. The only abnormal physical sign was bilateral papillœdema. Ventriculography showed a normal ventricular system. A diagnosis of toxic hydrocephalus was made. His eyesight became very impaired and about seven weeks later the ventriculogram was repeated, this time with Myodil (Fig. 6A and B). Again it was normal. A subtemporal decompression was performed to save the patient's sight. He returned to work for two or three months and then deteriorated. His other temple was immediately decompressed. Shortly after this he was seen by Mr. Harold Edwards who found signs of cerebellar inco-ordination and was convinced that the man had a cerebellar tumour. He was readmitted, a pitiful sight with both temples bulging grossly. There was still no hydrocephalus, but Myodil ventriculography showed the aqueduct kinked forward indicating a superior vermis tumour (Fig. 7A and B). Exploration revealed a very, very high vermis tumour which was partially removed. The patient succumbed. At autopsy the tumour was found to be an astrocytoma.



A B

FIG. 6A and B (*Case IV*, 21.1.52).—Myodil ventriculogram showing normal ventricular system.



A B

FIG. 7A and B (*Case IV*, 28.10.52).—Bilateral temporal decompression. Aqueduct kinked forward.

One could show many cases with posterior fossa tumours and absent hydrocephalus. One further example will suffice. It also illustrates the value and simplicity of the use of a small quantity of Myodil (Pantopaque) for the absolute confirmation of the diagnosis (Bull, 1950).

Case V.—J. M., a girl aged 18, gave a three-week history of headache and unsteadiness on her legs. She had also vomited several times. On examination, bilateral papillœdema and some unsteadiness of gait were detected. When admitted to hospital she had also developed some weakness involving the left VI and VII cranial nerves.

Air ventriculography showed a normal-sized ventricular system and a trace of air in the fourth ventricle showed this structure lying to the right of the mid-line (Fig 8A). In lateral view (Fig. 8B) the aqueduct appeared to be kinked slightly forwards. These findings were easily and quickly confirmed absolutely by the introduction of 2 c.c. of Myodil (Fig. 8C and D).

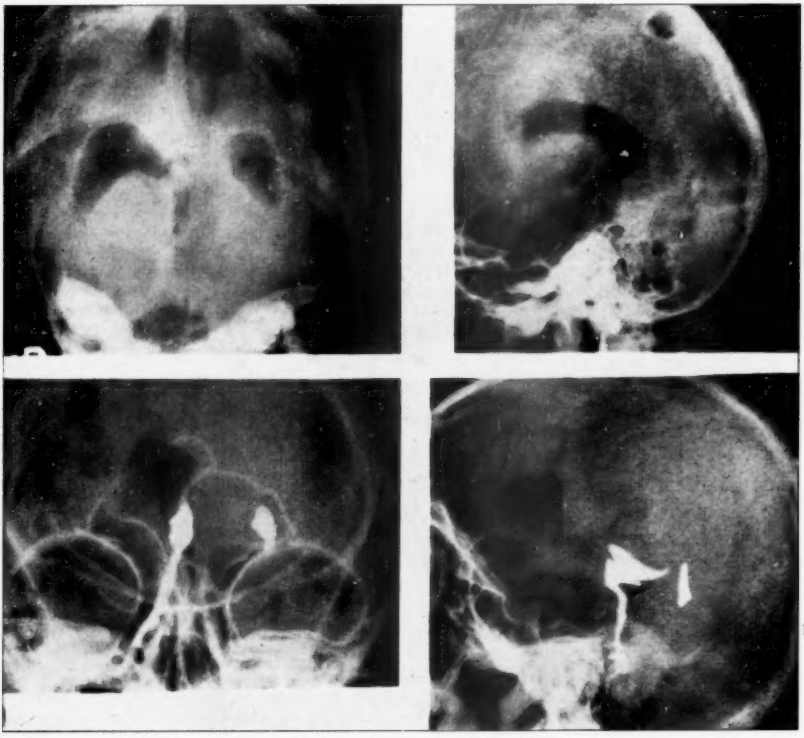


FIG. 8 (*Case V*, 14.10.52).—A, Trace of air in fourth ventricle which is displaced to right. B, Aqueduct ? kinked forward. No hydrocephalus. C, Myodil confirms deviation of fourth ventricle and also shows aqueduct displaced to right. D, Definite kinking of aqueduct. Operation: Left cerebellar hemisphere astrocytoma removed.

Mid-brain Tumours

Although it is still often assumed that a suspected case of tumour showing hydrocephalus at ventriculography has a posterior fossa tumour, the mid-brain must always be considered as a possible site.

Such mistakes should not be made if the radiology is carefully undertaken. Hydrocephalus can be caused by space-occupying lesions situated anywhere from the foramina of Monro backwards and downwards. Fig. 9 illustrates the more common lesions which may obstruct some part of

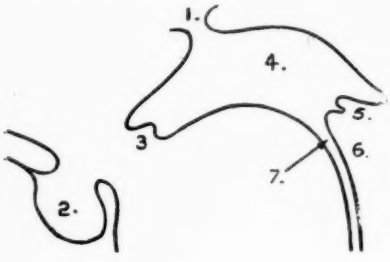


FIG. 9.—Hydrocephalus.

A. Partial or complete obstruction of the foramina of Monro.
   1. Colloid cyst of paraphysis.
   2. Sellar and suprasellar masses.
   3. Hypothalamic and chiasmatic gliomas.

B. Partial or complete obstruction and/or obliteration of the third ventricle.
   4. Thalamic masses.
   5. Pineal tumours.
   6. Corpora quadrigemina tumours.
   7. Aqueduct stenosis.

the third ventricle and so produce hydrocephalus. Often the clinical features of the case localize the lesion accurately, but by no means sufficiently consistently to eliminate negative posterior fossa explorations.

"Pineal" Tumours

When ventriculography demonstrates a mass in the region of the pineal gland the question arises whether a tumour or arachnoid cyst is present. The differential diagnosis is most important since a tumour is very difficult to remove and carries a high mortality. On the other hand an arachnoid cyst is quite benign and can be aspirated.

Radner (1951) found pathological vessels on vertebral angiography in 8 out of 11 tumours in the pineal region. Histological confirmation was obtained in only 2. Both were malignant gliomas.

When such a case fails to show pathological vessels it would seem reasonable to recommend surgical exploration with the hope that a cyst might be found.

Conclusions

Ventriculography is very reliable in localizing posterior fossa tumours. It may have to be augmented by Myodil ventriculography, particularly if the third ventricle is not dilated, and so makes manipulation of air through into the aqueduct and fourth ventricle difficult.

Often, however, lumbar encephalography might be used after air ventriculography and before Myodil. Only a few c.c. of air are necessary to outline the fourth ventricle and aqueduct.

If localization of a tumour, which appears to be removable surgically, is achieved then further radiology is meddlesome. If, however, the lesion appears to be inoperable from its position, but more knowledge of the pathology is needed for prognosis, then vertebral angiography should be considered.

If the ventricular system appears to be normal and yet clinically the patient is thought to have a lesion in the posterior fossa, again vertebral angiography should be considered.

Finally if radiology fails and the clinical evidence is strongly in favour of a tumour, exploration is probably indicated.

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Mr. Wylie McKissock: Much additional information regarding the extent and situation of a tumour can be obtained from ventriculograms and such information is of the greatest value to the surgeon in planning his operation.

I am in the habit of performing some 60 or 70 posterior fossa operations for tumour, or other space-occupying lesion, each year. In all cases, irrespective of the localizing value of clinical signs or straight X-ray changes, a ventriculogram is performed. Usually air suffices to give accurate localization of the lesion but, where it does not, then Myodil ventriculography is resorted to. Myodil, I may say, produces no immediate reaction or late sequelæ when injected into the ventricular system.

The result of ventriculography, whether with air or Myodil, has been to give such accuracy of localization as to render the use of the full cerebellar exposure unnecessary except on two or three occasions each year. In 96% of cases, therefore, a unilateral or mid-line incision only is made with saving of time and energy to the surgeon and his team and of discomfort to the patient. Convalescence from a mid-line or unilateral cerebellar incision is far less painful for the patient than a full curved cerebellar incision.

Whilst clinical localization of the acoustic neuroma is moderately accurate and straight radiography provides positive confirmation in a high proportion of cases, ventriculography still provides further evidence as to the size of the lesion and its main direction of growth, whether mainly lateral, or extending in front of the brain or passing upwards through the tentorial hiatus.

The real aim, however, when dealing with acoustic neuromata is to make the diagnosis and remove the tumour before there is any radiological evidence of its existence. Twice in my experience has it been possible to do this. The patients were suspected by Dr. Frank Elliott, on clinical grounds alone, to be harbouring such tumours and showed only involvement of the VIII nerve. Straight X-rays of the skull and ventriculography were entirely normal but the tests employed by Dr. C. S. Hallpike confirmed the clinical suspicion of acoustic neuroma. In each case exploratory craniotomy revealed a very small neuroma which was excised, with preservation of function of the VII and also of the VIII nerves.

Valuable, therefore, as is the aid which Dr. Bull can give us in the localization of tumours of the posterior fossa, I look forward to the day when radiology will have *no* part to play in the early diagnosis of tumours of the VIII nerve: the time at which they can be excised completely, in almost perfect safety and with the knowledge that the function of the VII nerve may certainly be preserved.

Dr. F. A. Elliott: Dr. Hamilton Paterson's reluctance to ascribe posterior fossa symptoms to a hypothetical "encephalitis" deserves praise, for—if we exclude the mid-brain lesions of Wernicke's encephalopathy, of polio-encephalitis, and of encephalitis lethargica—a diagnosis of "met-encephalitis" is seldom justified by post-mortem examination. To quote an illustrative case: a rather fat girl of 19 fell ill with a high temperature, extreme sinus tachycardia, tachypnœa, and rapidly advancing unconsciousness. The pupils were large, fixed, and equal, and before consciousness was lost there was paralysis of upward conjugate movement of the eyes. The upper limbs were held in extension and internal rotation, and the legs were extended, with extensor plantars. The spinal fluid was normal, as was a ventriculogram. Seemingly moribund she yet made a complete recovery in three weeks and returned to work for a year. She then had another attack, similar in all respects to the first, with features which again pointed to disturbance in the mid-brain and posterior end of the hypothalamus. This time she died, and was found to have a saccular aneurysm indenting the quadrigeminal plate in the mid-line—the sole pathological feature. Anyone seeing the girl in her first attack, and not knowing the sequel, would surely have carried away one of those dangerous "clinical impressions," viz. that here was a true encephalitis of the mid-brain.

Mr. Leslie C. Oliver: The use of Myodil in the diagnosis of tumours in the posterior fossa has considerably simplified operative technique; now it is always possible to make quick mid-line or lateral exposures instead of the time-consuming one through the curved transverse incision.

Dr. G. Pampiglione: A few points about electroencephalographic studies may be mentioned in connexion with Sir Geoffrey Jefferson's paper.

Posterior fossa lesions cannot be confidently localized by means of EEG in spite of occasional favourable reports in the literature. In fact, mid-line lesions do not show reliable differences in the EEG whether above or below the tentorium. Non-mid-line posterior fossa lesions either do not alter the EEG at all or give rise to generalized EEG changes that may not always be bilaterally synchronous.

From the work of the Fischgold team and particularly from the material I had the opportunity of studying at Queen Square from 1948 to 1951 it appears that a normal EEG in a patient with marked papillœdema is in favour of a posterior fossa tumour. The great majority of VIII nerve tumours do not alter the EEG, nor does any change appear a few weeks after a cerebellar vascular lesion or in small secondary deposits. In large tumours of the posterior fossa when the EEG is abnormal the brain-stem is involved or distorted; slow waves usually fairly regular and rhythmic appear symmetrically over the cerebral hemispheres. Sharp waves, spikes, or abnormal complexes are not seen.

The most important contribution of EEG studies is therefore in doubtful cases. In just over 10% of some 260 cases (from over 8,000 referred to the EEG Dept. at the National Hospital until 1951), in which a posterior fossa lesion was considered in the differential diagnosis, a unilateral EEG abnormality was found in the form of irregular slow waves or focal sharp waves. In this latter group operation or post-mortem revealed a unilateral supratentorial lesion usually alone, seldom in addition to some posterior fossa lesion.

With these observations in mind it appears that a lateralized EEG abnormality, particularly when the waves are irregular or sharp and focal, casts reasonable doubt on the presence of a posterior fossa lesion and may suggest a reconsideration of the patient's history and clinical signs, or the possibility of multiple lesions.

Mr R. T. Johnson: *Differential Diagnosis of Posterior Fossa Meningiomas.*—It is clear from our material (30 cases) and from Cushing's 23 cases (1938) that the first, and perhaps the greatest, difficulty is to recognize the presence of tumour at all, for in these two series original diagnoses included disseminated sclerosis (in 3 cases), syringomyelia, brachial neuritis, cervical neurofibroma, pontine glioma (in 2 cases), glioma of the corpus callosum, cerebral atrophy, encephalitis lethargica, trigeminal neuralgia (in 2 cases), and Ménière's disease. Meningiomas have been classified according to their site of origin, and although in the larger tumours this may not be possible to determine with any degree of accuracy the site of origin does bear some relationship to their mode of presentation, and I have divided them into four groups (Fig. 1).

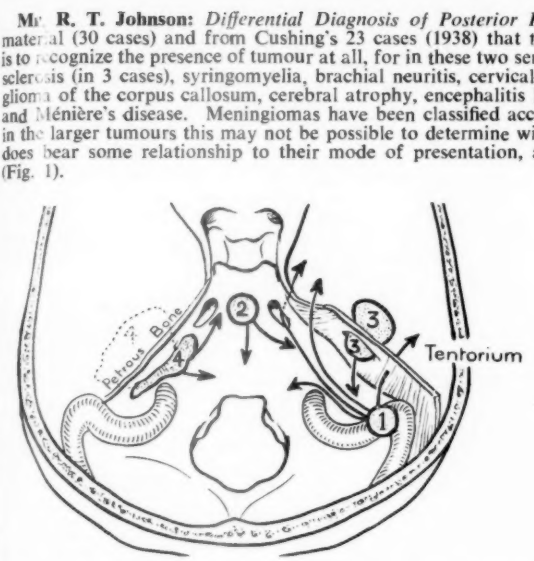

FIG. 1.—Meningiomas of the posterior fossa: Main groups. 1, Lateral recess. 2, Basilar groove. 3, Trans-tentorial. 4, Intra-petrous.

Group 1. Lateral recess.—There would seem to be no doubt that the commonest site of origin is the dura of the sigmoid and petrosal sinuses. From this point, tumour may grow medially over the convexity dura and indent the cerebellar hemisphere or down in the direction of the pons and cranial nerves or may grow up into the middle fossa between the free edge of the tentorium and the mid-brain, through Meckel's cave, or by breaking through the tentorium more laterally.

Group 3. Trans-tentorial.—These may arise on either side the tentorium and extend through it to a varying degree.

Group 2. Basilar groove.—The superiorly placed tumours form the clivus meningiomas, and the inferiorly placed the meningiomas of the foramen magnum; either may extend into the lateral recess and produce signs of a cerebello-pontine tumour. The upper group are usually mistaken for gliomas of the pons because the deep indentation of the brain-stem produces signs suggestive of a destructive process. In fact the raised iter and fourth ventricle seen in a ventriculogram may be indistinguishable from the appearances produced by a pontine glioma, and even at exploration the elevated floor of the fourth ventricle supports the diagnosis of an intrinsic tumour. This particular difficulty encouraged us to seek better means of differentiation and although some success has been obtained, accurate diagnosis will not have great importance until advances in technique render clivus meningiomas more amenable to surgery. The lower group present as spinal tumours, syringo-bulbia, disseminated sclerosis, brachial neuritis and will be diagnosed at exploration or by myelography.

Group 4. Intra-petrous.—These cause destruction of the petrous bone and multiple cranial nerve palsies, especially of the VII, VIII, IX, X, XI and XII nerves. The first symptom is usually a facial palsy, the history is long, and some have had vascular polypi in the ear. There is some question as to the nature of this group of tumours, for there is no doubt that glomus jugulare tumours, angioblastic meningiomas and angio-endotheliomas are diagnoses variously applied to tumours having a common symptomatology and similar histological features. Diagnosis presents no difficulty for plain X-rays show gross petrous destruction. It should be pointed out that 2 of the 3 cases described as clivus meningiomas by Campbell and Whitfield (1948) would be regarded by us as coming within this category for they showed gross petrous destruction. As these tumours in their forward extension involve the basisphenoid eventually they do lie anterior to the pons although the greater bulk of the tumour is extradural and the layout is very dissimilar to that illustrated by Cushing as typical of tumours of the basilar groove.

The tumours of the lateral recess and of the tentorium will be considered, in a little more detail.

Group 1. Lateral recess.—Some of the meningiomas grow medially and soon encroach upon the cranial nerves which they involve in a less regular manner than do the acoustic neuromas. The V nerve was involved in half the cases and most commonly the second division (a depressed corneal is probably of no localizing value; so frequently was it bilateral). True trigeminal neuralgia, however, only occurred in 2 cases, both were second division and 1 varied according to the patient's posture. In 3 other cases there was a neuralgic pain in the face on coughing, and in a further case there was a sudden onset of numbness in the left upper canine tooth which later spread to involve the whole face. The second division of the V nerve was involved most commonly and after that the upper half of the face, that is the whole of the first division and the upper part of the second. Paralysis of the VI nerve proved to be a true and not a false localizing sign in every case and indicated a clivus meningioma or an extension of a recess meningioma under the pons; it was from the surgical viewpoint a

grave omen. Slight paresis of the VI nerve occurred in only 2 other cases: in 1 of these there was an extension of meningioma through the tentorial hiatus and in the other a large trans-tentorial meningioma. The VII nerves were involved rather more commonly than VIII, but the involvement was mostly slight and it is of interest that at operation the VII and VIII nerves are, characteristically, unseparated and will be seen curving round the posterior aspect of the tumour. Small meningiomas may occur at the porus producing vertigo and deafness as the only symptoms and one such case was discovered at operation to divide the VIII nerve for typical Ménière's disease.

Other meningiomas do not involve the cranial nerves and may grow silently, burrowing into the cerebellar hemisphere until they are of a very considerable size, ataxia neither being very prominent, nor very early in onset. The reason for this may be that these tumours tend to grow behind or in front of the cerebellar hemisphere, or if they extend medially they do so by irregular feathery or flattened processes which push behind or in front of the pons. The indentation and angulation of the pons so characteristic of the more globular encapsulated acoustic neuroma and the cause of the severe disability is rarely produced by a meningioma.

Group 3. Trans-tentorial.—These tumours lying in the No Man's Land between the cerebrum and cerebellum have proved to be the most difficult of all to diagnose. If there were a clinical syndrome it would be a slowly progressive hemiparesis, perhaps associated with epileptic attacks but accompanied by slight bilateral ataxia, so that the disability is always greater than one would expect from the physical signs. Nystagmus has not been present in all our cases and papillœdema has developed extremely late. In some of the cases the V nerve was involved. L.P. pressure and the C.S.F. may be normal and ventricular studies may be surprisingly normal even when the tumour is of considerable size. One of our cases had a normal encephalogram but as one year later the hemiparesis was more marked the air encephalogram was repeated, but no air entered the ventricular system: four hours later she suddenly died and at post-mortem there was an enormous tumour of the tentorium. In fact, where there is a possibility of a tentorial meningioma a failed encephalogram should be regarded with extreme suspicion, the ventricle tapped and ventricular studies made, preferably by the introduction of Myodil. The slight reaction Myodil sometimes causes does not worsen the patient's condition; Myodil is not dangerous in cases of high pressure in contradistinction to air, and careful observation of the shadow as it moves through the ventricular narrows may reveal multiple lesions and minutiæ of pathology which might well be missed by air studies. The signs of a large tentorial meningioma are elevation of the inferior horn (Ruggiero and Vastellano, 1952), obstruction of its temporal tip, and not only kinking and narrowing of the iter, but elongation as the tumour separates the cerebrum from the cerebellum (Fig. 2).

FIG. 2.—Tentorial meningioma: Myodil ventriculogram. The iter (arrow) is kinked, narrowed and elongated; the inferior horn is elevated, narrowed and partially obstructed causing expansion of the tip (dotted).

In conclusion a knowledge of the possibilities will enable meningiomas to be suspected in patients presenting in a variety of ways in which mental changes may be striking and yet ataxia and nystagmus not marked. Plain X-rays may show: (1) Calcification in the tumour, (2) Petrous erosion and (3) Occipital endostosis.

The C.S.F. protein may be raised and in our 30 cases averaged 60–85 mg.%. The limits, however, were 35–400 mg.%. The EEG may show an occipital focus and lead to a suspicion that a cerebellar tumour is extending upwards. Air encephalography may be dangerous and the displacement of cisterna ambiens (Robertson, 1946) may be very slight and give little indication of the enormous size of the tumour; Myodil studies are more helpful. Angiography would doubtless have been diagnostic in some cases although pre-operative diagnoses were such that other investigations were done in preference.

By using modern methods of anæsthesia, the sitting posture, or chemical hypotension as circumstances direct, and doing a combined operation by dividing the lateral sinus, completely dividing the tentorium and displacing the occipital lobe upwards and the cerebellum medially, it is possible to remove surgically some of these tumours which otherwise have such a bad prognosis.

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Section of Anæsthetics

President—M. D. Nosworthy, M.A., M.D.

[*April* 10, 1953]

DISCUSSION: ARE ANÆSTHETIC RECORDS WORTH KEEPING?

Dr. William W. Mushin: Our President, Dr. M. D. Nosworthy, has done more than any other man to awaken anæsthetists to the value of keeping records. In spite of his work for the last thirteen years, anæsthetists in this country do not yet regard record keeping as much more than a hobby. Unlike our American colleagues, they prefer to rely on their impressions; these can be very wide of the mark when the latter is determined by proper statistical analysis. As an example of how records are regarded across the Atlantic, here is a question set by an American colleague in an examination paper for postgraduates attending the World Health Organisation Anesthesiology Centre in Copenhagen. The candidate had to indicate which answer was the correct one.

"A well-kept anæsthesia record

(*a*) demonstrates the artistic ability of the anæsthetist;

(*b*) helps the anæsthetist to pass the time while squeezing the bag;

(*c*) helps to support the paper industry;

(*d*) by its very production contributes to the well-being of the patient, is an aid to the surgeon in his further care of the patient; helps the anæsthetist in his evaluation of the drugs he uses, the techniques he employs, and the abilities and knowledge he has or does not have, and in a course such as this, is an obligation which each anæsthetist has to his fellow trainees so that all may share to the fullest extent many more experiences in anæsthesia than could be encountered on an individual basis in the same length of time."

The term "anæsthetic record" may be applied to any collection of data about an anæsthetic. This record may in fact, vary from nothing more than the simplest facts — the patient's name, age, sex, date and nature of operation and anæsthetic — to an elaborate detailed description of one particular part only of the whole anæsthetic procedure.

Firstly, there is the record which is intended to provide the anæsthetist himself with information about his personal activities. While such records may give a picture of the professional activities of an individual anæsthetist, they very rarely provide information about either a cross-section of anæsthetic work or of a cross-section of the public. In addition, the terminology used will probably be intelligible only to the anæsthetist himself, and since there is no check, inaccuracies may be high in number.

Secondly, there are the records which are kept to provide interest and information to the anæsthetist while he is actually working in the operating theatre. Such a record generally concentrates on observations made at the time rather than the inclusion of data about the disease, or about the physiological state of the patient before and after the operation. Such records are of strikingly little value in that they tend to consist of little more than a blood pressure record. This, by itself, tells very little when studied at some later date, as only the man on the spot can even attempt to diagnose the real cause of a rise or fall in blood pressure.

Thirdly, there are the records which are going to form the basis of a regular comprehensive report about the anæsthetic work in a particular hospital. When such records are kept well and are properly designed and reported on, they form a very valuable addition to anæsthetic experience in general. They give information about the frequency of use, the virtues and the vices of anæsthetic techniques, as well as how they are applied to different types of operation and to different types of people.

The fourth group is an elaboration of the last. It consists of records sufficiently detailed in the information they contain to allow of the investigation of and reporting on more precise interrelationships of various factors. Such records could show, for example, the hospital death-rate of various groups of patients, having different anæsthetics and for different operations, or, again, they could indicate not only how one anæsthetic or one kind of technique waxes and wanes in favour during the months or years, but perhaps also the causes for these changes in popularity. These records could give information on the incidence of different types of complications with different anæsthetics and how this incidence is related to other factors connected with the patient and his disease. In a teaching hospital, the kind of cases used for teaching and the kind of anæsthetics taught to students would be clearly shown, as also whether patients suffered any harm thereby.

Lastly, there are the records which are intended to furnish an answer to a particular problem in research. If this is the purpose of the record, then I would like to emphasize that the problem should be formulated first and the record and its manner of completion designed afterwards. It is very rarely that records designed with no particular problem in mind except that "something interesting might come out" ever do provide a definite answer.

The various people to whom these records are likely to be of value are firstly, the hospital authorities. Just as the administration needs data about other branches of medical work, so it needs information regarding anæsthetics. No proper estimates of staff, materials, instruments and standards of work can really be made without it. The clinical and professional stature of anæsthesia in the eyes of the administration, a not unimportant thing, is enhanced by good record keeping.

Secondly to the patient and the anæsthetist. At the present time, little more than lip service is paid in this country to the belief that a record kept at the time of the anæsthetic has any value in the management of the anæsthetic. I believe that keeping a record of every patient materially helps me to give a safer and more efficient anæsthetic. It is my own practice and teaching that at least the blood pressure and pulse should be taken and recorded for every patient who has an abdominal, thoracic or neurosurgical operation, for every patient who has a blood transfusion and for every patient having any operation which could reasonably be called "major." By making and recording his observations throughout the anæsthetic, the anæsthetist not only receives valuable information about the state of his patient, but the latter is still further safeguarded from lack of attention and observation on the part of the anæsthetist.

Thirdly, the surgeon benefits from anæsthetic record keeping. He is happier and more relaxed when he knows that his patient is under constant observation, and that the details of the anæsthesia will be available for later reference and discussion. It is likely that his reasonable question, "How is the patient?" will be answered with more true confidence in these circumstances than it could be with only a finger on the pulse and glimpse of the pupil to go by.

Once we are agreed on the value of such objective recording during the administration of the anæsthetic, I would suggest that the type of record to be used is the one which will allow a reasonably comprehensive yearly report on the anæsthetic work of the hospital to be drawn up. Anæsthetists would then be able to provide data about their hospital's anæsthetic work even though it had been performed by a number of anæsthetists. The numbers of patients in the aggregate will be large, errors of observation will tend to be neutralized and each year a large amount of factual information about the anæsthetic work in this country will be in existence.

The sorting and checking of records are best done mechanically by systems like the Hollerith, and such methods would become available if routine hospital recording became widespread. When it is realized that it is possible to include nearly two hundred isolated facts selected out of nearly a thousand on each Hollerith card, it will be appreciated how detailed such a record

can be. That the keeping of such a record is not a time-consuming or complicated matter, will be made clear by Dr. Rendell-Baker's account of the method used in our own teaching hospital.

If records are to be of any value, they must be all inclusive; whether they are hospital records or personal records or records in connexion with a research problem, every patient must be included. The temptation to omit records of perhaps short and apparently unimportant cases or the records of cases of one's pet method which did not go well or had complications, is a great one, and only some foolproof check system will prevent this all-too-human lapse. Our own self-imposed discipline is not only to have the records in charge of the hospital Records Department, but to have a separate check made by that department to ensure that every single patient who has had an anæsthetic also has a record.

Another part of anæsthetic record keeping involving a human factor is the completeness and accuracy of the record. In order for accurate information to be recorded about the whole anæsthetic, the data must be gathered by anæsthetists. An important part of the work of our junior staff, and even of ourselves, should be the collection of this data. I know this involves visiting the patient beforehand and visiting him at least once or twice after the operation until the effects of the anæsthetic can be reasonably considered to be over. In most parts of the country, time is allowed for anæsthetists to work outside the operating theatres. The production of anæsthetic records which contain the results of their observations should be a natural result of this work.

A criticism of anæsthetic records is that the words used by one anæsthetist to describe what he sees have a different meaning to the same words used by his colleague. This is avoided by simplifying the factors to be recorded and by adopting some agreed terminology. Thus a cough is probably called a cough anywhere in the country, vomiting means vomiting everywhere. Any adjective applied to these terms should be strictly quantitative rather than qualitative. It should be the aim of the anæsthetist in designing the record, to use terms about which there could be no doubt to anyone considering the record at some later date. In the evolution of our own record system we have paid particular attention to this point, and we are now reasonably sure that the terms we use now will still be accurately understood in ten years' time. Nevertheless records have their limitations. It is better to record the number of people who had a cough, than to try and differentiate between those that had a hacking cough or a brassy cough or a booming cough.

What to Record

Leaving out the special type of record applicable to the investigation of a particular problem, in general, the record should contain information primarily of interest to the particular hospital and anæsthetist. It is unlikely therefore--and from many points of view undesirable—that records from different parts of the country should exactly resemble each other. Nothing is more inimical to the success of country-wide anæsthetic recording than trying to force clinical anæsthetists to record data which they feel themselves is worthless. On the other hand, so long as there is agreement on terminology, there would be a good deal of common data collected which would enable very wide surveys to be possible.

It should not be forgotten that the anæsthetic record in a hospital forms part of the patient's general record and should therefore be related to it. The sort of link and the amount of overlap between the information on the hospital record and that on the anæsthetic record is best determined after consultation with the hospital Records Department.

Proper analysis is essential if worth-while conclusions are to be drawn from the collected data. The collaboration of a professional statistician is necessary, in the case of a busy hospital, if the best use is to be made of the energy expended in keeping anæsthetic records. In our own case, it was only after many months of constant discussion with Dr. Lewis-Faning, the statistician to the Welsh National School of Medicine, that the form the record was to take was decided upon. Even then extensive annual revision took place for the first few years. We found that the possibilities of the Hollerith system, as well as the limitations imposed by it had to be well understood before the record could be designed. Such important points as what kind of sorting machine was available, even the arrangement of the typescript on the records to make the work of the punching clerks easy, had to be considered. Without the help of an expert statistician, the compilation of a proper report and the making of reasonably accurate deductions, is difficult, if not impossible, to the average clinical anæsthetist without special training. Nevertheless, a statistician without an anæsthetist at his side might make as many blunders or worse ones than an anæsthetist without a statistician. We have heard that in the former circumstances at one centre, acute retention of urine was reported as a frequent complication of Trilene, until analysis showed that the patients concerned had all had cystoscopies!

When many thousands of records are being handled yearly, a mechanical system of recording and sorting the data is essential, also the services of a statistician. We have found that systems designed for hand sorting, such as the Copeland-Chatterson type of card, tend to break down when such large numbers are being dealt with.

The Records Department

Every hospital has a Records Department. If it is accepted that the anæsthetic record is a part of the patient's general record, then the hospital Records Department should take a very active part in the collection of such data. Anæsthetic records may necessitate clerical assistance; they will certainly need cabinets and cupboards for their storage. All these pose problems which can only be satisfactorily solved if the hospital Records Department exercises the same supervision and interest in anæsthetic records as it does in hospital records. The hospital Records Department will also devise what information should be duplicated on the anæsthetic record to provide a link between it and the patient's general notes. It may be convenient if the anæsthetic records are kept in separate filing cabinets. This should not, however, lead anæsthetists to make the fundamental error of regarding the anæsthetic records as their own private property and something unconnected with the patient's general records. The two are part and parcel of the same thing.

Summary

There are several types of anæsthetic record. All are worth keeping if they are well designed and if they are accurately kept. The most important type of records are those from which a comprehensive hospital report can be drawn up. It is my belief that such records should become universal. They are essential for any accelerated advance in anæsthesia. Expert statistical and clerical help will be needed in large hospitals to assess the record cards.

Dr. L. Rendell-Baker: I propose to give some details of the system of anæsthetic records we use at Cardiff.

For some years before we evolved our present system, we kept records on the Nosworthy card. These were made out, slotted, and filed entirely by the anæsthetists. We could not check on the number of cards lost, the correction of errors of slotting was difficult, and the number of variables that could be coded was limited. Finally, when faced at the end of the year with the sorting of between 4,000 and 5,000 dog-eared cards which refused to fall out when shaken, our courage failed and we looked around for a more satisfactory method.

Our anæsthetic record system is now run under the general supervision of the hospital Records Department. They provide an independent check on the accuracy of the record keeping, and ensure the satisfactory completion of a record for each patient.

A record starts the evening before the operation, when the anæthetist makes his pre-operative round and enters details of the patient's condition and the premedication ordered. Attached to the patient's notes, the record comes down to the theatre with the patient the next day. Here details of the anæsthetic and of the operation are recorded and the sheet left in a "letter box" provided for this purpose in the theatre. The next morning the records clerk goes to each of the theatres and makes a list of the patients operated upon the previous day, giving each patient a serial number. The record sheets in the letter box are collected and checked against this list. Any deficiencies are at once apparent and the anæsthetist concerned is requested to complete a card without delay. Index cards for each patient on the list are typed by the clerk as a cross check and these remain in her "current" file until the record is returned with the "follow-up" completed. The anæsthetist collects his records from a pigeonhole in the Anæsthetic Department before making his post-operative round. Cases are followed up until discharged from hospital or until the anæsthetist feels that the patient has recovered from the anæsthetic. The records are checked again when the patient is finally discharged to eliminate any error in follow-up.

Now to deal with the clinical record sheet itself. As the Hollerith system was already in use in our Medical School, this appeared to be a very good system on which to base our own clinical record sheet, enabling as it does nearly 200 factors to be coded out of nearly 1,000 for each patient.

Our next problem was to find a convenient method of transforming clinical notes into precise statistical data. In America, rather bulky code books are widely used for this purpose. Each clinical fact is allotted a code number by reference to the book. As you can imagine, this is a somewhat lengthy and tedious process, and we doubted whether it would be possible to persuade our colleagues to undertake this drudgery! Instead we decided to use a self-coding sheet, on which were printed all the factors of interest to us. This is a double 10 in. by 8 in. sheet which is folded for ease in carrying in the pocket. To illustrate the general principles of our method I will select one or two items from the sheet.

The front page is devoted to the diagnosis and pre-anæsthetic complications. The anæsthetist is presented with a dozen or so complications under various headings (e.g. respiratory, alimentary, etc.) from which to choose. The mere act of ringing each one chosen indicates to the clerk the code figure to be punched.

Of the two centre pages one side is devoted to the premedication and the site, nature and duration of operation. The premedication section (Table I) has been divided into two, the

TABLE I

PREMEDICATION

AGENT A	DOSE:	TIME:
0 None		
1 Atropine		
2 Scopolamine	gr 1/160	1 pm
3 Others (specify)		

Add X if premedication repeated
Add V if premedication unsatisfactory

34 2

AGENT B	DOSE:	TIME:
0 None		
1 Nembutal (oral)		
2 Seconal		
3 Thiopentone (rectal)		
4 Other barbiturate		
5 Bromethol		
6 Chloral hydrate		
7 Paraldehyde		
8 Pethidine		
9 Others (specify)		
X Morphine		
V Omnopon	gr 1/3	

35 V

belladonna compounds and the sedatives. As morphine and Omnopon are sometimes combined with a hypnotic such as Nembutal or chloral hydrate, we have coded the former X and V, because in our system either of these letters may be punched in addition to one of the numbers in each column on the Hollerith card. We are therefore able to code three drugs in the premedication section. The code letters X or V have been given throughout the whole sheet to items which commonly occur in combination with others.

On the opposite centre page, details of the anæsthetic technique and any complications are recorded. For example, in the section on inhalation technique for general anæsthesia (Table II) assisted or controlled respiration may be coded in addition to the method of anæsthesia used. Similarly the type of endotracheal or endobronchial tube used may be indicated and also whether a cuff or pack was employed. When a whole section is not applicable, the anæsthetist simply strikes it out and it is coded as nought by the clerk.

On the back page are recorded the post-operative complications, post-operative treatment and duration of stay in hospital.

The actual insertion of these code numbers in the spaces provided is done by the record clerk. Thus relieved of time-consuming clerical work, the anæsthetists are able to devote their time to the observation of their patients. A senior registrar sees all the records before they leave the anæsthetic department to eliminate as far as possible errors in recording of clinical details.

At convenient intervals, usually every three months, batches of these clinical records are sent to the Statistical Department, where Hollerith punch cards are prepared from the data recorded on them. The clinical records are returned, but the Hollerith cards remain with the statistician to be available for immediate sorting should any problem arise. To give an idea of the speed

TABLE II

INHALATION TECHNIQUE:

0 No inhalation
1 Open drop

2 Insufflation
3 Valveless method
4 Partial rebreathing (e.g. Boyle's app.)
5 No rebreathing (e.g. Oxford vap.)
6 Intermittent flow apparatus
(7 Absorption—To and Fro)
8 Absorption—Circle
9 Others (specify)
X Assisted respiration
(V Controlled respiration)

54 √7

ENDOTRACHEAL AND BRONCHIAL TUBE

0 No tube
(1 Orotracheal—direct vision)
2 Nasotracheal—direct vision
3 Nasotracheal—blind
4 Armoured oral tube
5 Bronchus blocker + oral tube
6 Endobronchial tube
9 Others (specify)
(X Cuff)
V Pack

55 X1

and facility with which this can be done, out of the 5,000 cases anæsthetized in a year, one could easily determine the number of patients given, say, Trilene anæsthesia, in twenty minutes. Naturally, to include other factors would take a little longer, but it is quite feasible to obtain full data on a problem very quickly without upsetting either the routine of the Anæsthetic Department or unduly troubling our colleagues in the Statistical Department.

For the records and their statistical data to give good value, the system must be watertight with every possible safeguard against inaccuracy.

Our own experience has been that once the initial difficulties—when the system is started—are overcome, the daily routine becomes completely acceptable, and is as much a part of the anæsthetic as the premedication.

Dr. M. D. Nosworthy: I entirely agree that the detailed sorting of *large* numbers of records is more satisfactorily managed by a mechanical system than by the needle-sorting of punch cards such as I use. When I started keeping anæsthetic records, however, there was little opportunity of comparing my own with anyone else's. I therefore concentrated on studying the patient's response to different anæsthetic techniques and to various surgical procedures, and I tried to discover whether there was any correlation between disturbances during anæsthesia and post-operative complications. The Copeland-Chatterson system—with all the data on the same card—proved very satisfactory for this purpose. A well-kept record should picture the patient's state, and what the surgeon and anæsthetist are up to, all through the operation; and the study of such records at leisure afterwards has taught me a great deal—in fact, most of the things which I have written about have been based on observations culled from my own records.

I regret to have to say that the paucity of information often recorded and the discrepancy between individual recognition of disturbances during anæsthesia, as well as the varied criteria for assessing post-operative complications, has made me chary of other men's records. In fact, I have never been finally convinced that the information which can be obtained with any certainty from group-records, so detailed as those used at Cardiff and elsewhere, justifies the labour involved. I personally have reduced *routine* pre- and post-operative data to the broadest terms because I have come to the conclusion that—if a salient point is not to be missed—each special investigation calls for a series of observations especially designed for that particular study.

I hope that these excellent papers will stimulate more groups to keep communal records on all cases; but men who are not interested do not make worth-while records, and unless such group-records are accurately and uniformly kept the prime value of records will, in my opinion, prove to be what each man learns through the years from his own, for the ultimate benefit of his patients—and this can be a great deal.

Dr. H. J. V. Morton: I agree with Dr. Mushin on the value of anæsthetic records for educational and administrative purposes, though for these uses some simple system is adequate. But I am not at all happy about the results which may follow the unqualified use of complicated routine records for purposes in any way connected with "research." And, having been to the great trouble and expense of collecting data in the manner Dr. Mushin and Dr. Rendell-Baker have described, who could resist the temptation to draw inferences from them? There are at least three serious objections. The first is summed up in the dictum ". . . a record cannot give information on a question which was not in the observer's mind at the time the observation was made". If it were possible to record the answers to hundreds of routine questions in would be probable, at the end, that some unrecorded feature would turn out to be the matter of prime importance.

We may by chance escape this difficulty, but we still have to face the second. What reliance can be put on observations made by *different* people? There are very few measurable things in clinical anæsthesia, at the present time. There are few variables, but many attributes. Now although among the latter we can agree on the age and sex of a patient, and whether he is alive or dead, there is little else which lends itself to rigid classification. The extent to which most phenomena are present or absent has to be a matter of opinion. The provision of definitions and criteria, even if our colleagues understand, accept, and conscientiously abide by them, cannot improve the situation very much, since various contributors will bring to bear various amounts of experience, medical knowledge, and observational diligence.

There are some situations in which even both the foregoing objections might be overcome but the third one offers greater difficulty. No one will deny that the biological material with which we, as anæsthetists, have to deal possesses inherent variability to a remarkable degree. How can we hope to avoid error except through the accepted method of the planned controlled experiment? Yet how often can the conditions for such an experiment be reproduced by the manipulation of routine records at some later date? How often can even the single most important and elementary condition be satisfied, i.e. the *random* allocation of patients to comparable groups under study at the same time?

Where there is sufficient medical man-power the keeping of routine anæsthetic records is doubtless a beneficial exercise, but the findings from such records can rarely be of more use than to point the way to, and serve as, subject matter for subsequent planned investigations. In most hospitals medical man-power is limited. Under these circumstances it seems to me that when time can be found it is better to spend it keeping records concerned with the elucidation of specific clearly defined problems.

Dr. P. J. Helliwell: Our experience at Guy's Hospital bore out many of the points made by the opening speakers. A very determined effort had been made to keep records of all anæsthetics using the Nosworthy card index system, but the system broke down because:

Firstly, unless at the time the record was made the anæsthetist knew for what particular purpose it would be required it was almost impossible to obtain reliable information from it.

Secondly, despite every effort many anæsthetics did not have a record kept and therefore any general summary was valueless.

Thirdly, any attempt to obtain information from large numbers of Nosworthy cards, and the process of re-sorting them into serial order, was a time-consuming and laborious procedure.

At present, records are only kept at Guy's Hospital for a special series of cases, concerning which we wish to gather certain information.

Dr. C. E. Sykes: At the Manchester Royal Infirmary, we have, for several years, kept an anæsthetic record card for every in-patient to whom an anæsthetic has been administered. One method in use for several years had finally to be abandoned for financial reasons and at present the Nosworthy card is employed. If it is desired to carry out a particular piece of research, one feels that it is necessary to know the type of information which will be required and to make quite certain that such information is recorded in each case. If one expects to find such items recorded in the card used on "routine" cases, then one will surely be disappointed. Recordings made while working through a long list, single-handed, frequently have several possibly important omissions.

In addition to the anæsthetic record card, an operation register is kept in which every operation is recorded, together with the type of anæsthetic employed. These records go back as far as 1870.

Dr. R. P. Harbord: I agree that anæsthetic records should be designed for a particular purpose. Whatever the method chosen, the essential is clear documentation. In the record system which Dr. Mushin uses at Cardiff, I would suggest that instead of the heading "Shock", anæsthetists should write whatever they mean by this, e.g., pale face, rapid pulse, and hypotension, including the extent of these findings whenever possible. Similarly, the diagnosis of "chronic bronchitis" might be made either by a skilled clinician or by a medical student, and it would be of greater value if the signs and symptoms which have been observed were documented, e.g. pyrexia, cough, sputum, dyspnœa, or sonorous rhonchi heard in the chest, together with any relevant negative findings.

Records expressed in such a way would be far more intelligible when examined at a later date than those containing the diagnosis alone. They also allow useful comparisons to be made with the data obtained by other workers. I favour the use of a blank sheet of paper, the back of which is covered with data relevant to the problem to serve as a reminder of what to look for.

Dr. J. D. Laycock: The keeping of anæsthetic records has a value apart from statistical research. For medico-legal reasons a record of every anæsthetic may be useful if technical mishaps are recorded, such as the inadvertent leakage of thiopentone around a vein. Surgeons who write up cases for publication are apt to ask for details of the anæsthetic many months later. Records of anæsthetics for plastic surgery can be very instructive if several operations are performed on the same patient as different drugs and techniques can be used and compared with greater value in such cases.

Section of Radiology

President—CONSTANCE A. P. WOOD, M.A., M.R.C.P., F.F.R.

[*January* 16, 1953]

Tabetic Spinal Arthropathy

By H. W. HOLLAND, M.B., M.R.C.P., D.M.R.

Manchester Royal Infirmary

ARTHROPATHY as a complication of tabes was first described by Charcot in 1868.

The majority of the arthropathic joints are associated with tabes and syringomyelia but the condition also occurs as a complication of cauda equina lesions, transverse myelitis, traumatic paraplegia, leprosy and, as has recently been emphasized, diabetic polyneuritis.

The usual figure for the incidence of an arthropathic joint of the leg complicating tabes is 6–10%, and the complication is clinically obvious.

It appears to me, however, that tabetic arthropathy of the spine is less widely recognized both as a clinical and radiological entity. It may be that tabetic patients tend to gravitate to neurological rather than orthopædic clinics, but even Kinnier Wilson in his Textbook of Neurology (1940) gives spinal arthropathy scant attention and considers it a rarity. It is of interest in this context to mention that last year a case of arthropathy of the spine was reported as a complication of a severe diabetic polyneuritis. The condition was described by Zucker and Marder and this apparently was the first case of its kind to be reported.

It is difficult to come to any accurate assessment of the incidence of spinal arthropathy in tabes. As I shall show later neither symptoms nor signs may be particularly obtrusive and it is unlikely that the spine will be singled out for special scrutiny when a tabetic patient is examined. Garvey and Glass (1927) say: "While reports of the affection are relatively few, it is our opinion that the condition occurs more frequently than has been observed. Unknown to the patient, because it gives him no symptoms and unrecognized by the physician who usually makes no special examination of the spine . . . we feel it frequently eludes diagnosis."

Although I do not agree with the statement that the spinal arthropathy is entirely symptomless, it is certainly true to say that the radiological picture may be very much more severe than the symptoms would suggest and this is an important point to have in mind.

The first account of spinal arthropathy is due to the German physician Kronig, who published a paper called "A Case of Spondylolisthesis in a Tabetic" in 1884. Kronig's case concerned a man of 35 with a ten years' history of tabes who injured his spine and within a few months developed a severe spinal deformity with abnormal mobility. The condition was stated to be painless. Abadie (1900) had a series of 14 cases in 4 of which there were post-mortem examinations. Steindler *et al.* (1942), Garvey and Glass (1927) and Pomeranz and Rothberg (1941) all agreed that spinal arthropathy was commoner than had been generally thought. They systematically X-rayed large numbers of tabetics regardless of symptoms and this probably explains their findings. A detailed radiological account of the condition was published by Pape in 1929. The cases that I have seen confirm the essential points of this description.

Radiological features.—The site of election is the lower dorsal and lumbar spine. The disease is rarely found elsewhere. Probably the increased stress to which this part of the vertebral column is subject explains this finding.

Basically localized and diffuse forms of the disease, either with bone atrophy or hypertrophy, may be distinguished, although perhaps a mixed picture with a combination of destructive and formative changes will be present. Thus it is seen that the changes are analogous to the peripheral arthropathies.

The bone hypertrophy gives the vertebræ a massive, dense appearance. Local bony outgrowths also develop which have aptly been described as "les becs de parroquets" by the French authors. Narrowing of the intervertebral disc spaces is another important feature. The bone destruction leaves ragged and uneven vertebræ and this effect is exaggerated by secondary new bone formation.

Any variety of vertebral deformity may develop including spondylolisthesis and pathological fractures although some degree of kyphoscoliosis is probably commonest.

In some cases paravertebral calcification akin to the juxta-articular calcification in peripheral arthropathies is present which increases the difficulty of diagnosis.

Some authors have described a variety of arthropathy characterized by diffuse osteoporosis without any other changes. I have not come across this condition myself. It is possible that this was a simple disuse atrophy and not a true tabetic process.

Figs. 1, 2 and 3 are taken from Abadie's paper (1900, p. 116, plates XVIII and XIX). They show the site of the lesion, the vertebral destruction and irregular appearance, the spinal deformity, and the hypertrophic changes.

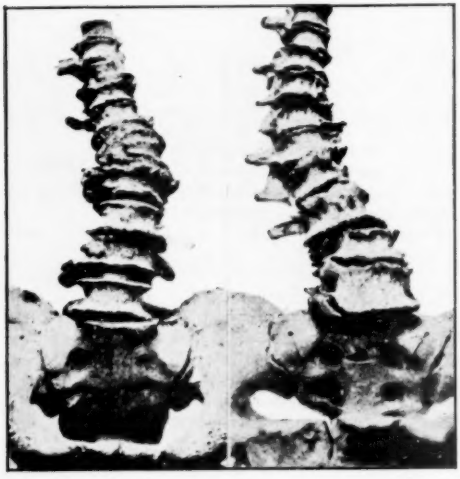


FIG. 1.

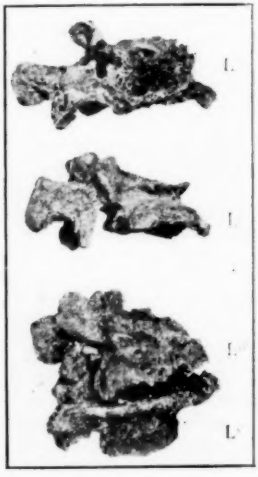


FIG. 2.

FIG. 3.

FIGS. 1, 2 and 3.—Reproduction of specimens from Abadie's paper showing the destruction and deformity produced in the spine.

Symptoms.—Although the spinal condition may be entirely symptomless, backache and root pains are a common feature. It must be borne in mind that the backache and root pains may be submerged amongst the many other tabetic symptoms and direct and leading questions may be necessary when taking the history. On the other hand, the spinal symptoms may be severe and disabling. In one of the cases I saw there was also local pain and bony tenderness, which were furthermore the presenting complaints.

In the differential diagnosis the following conditions, amongst others, should be considered: (1) Hypertrophic osteoarthritis, (2) tuberculous disease of the spine, (3) chronic low-grade osteomyelitis, (4) Paget's disease.

I hope to be able to show in my cases that the radiological features are quite distinctive.

In the last fifteen months, I have seen altogether 5 cases. In 4 of these the diagnosis of tabetic arthropathy is highly probable. In the fifth case it is likely, although as yet early changes only are present. There are 3 males and 2 females, ranging in age from 42 to 67. In 4 cases the diagnosis of tabes was known at the time of X-ray examination. In 1 case the spinal condition was a chance finding and the presence of tabes was thereafter confirmed.

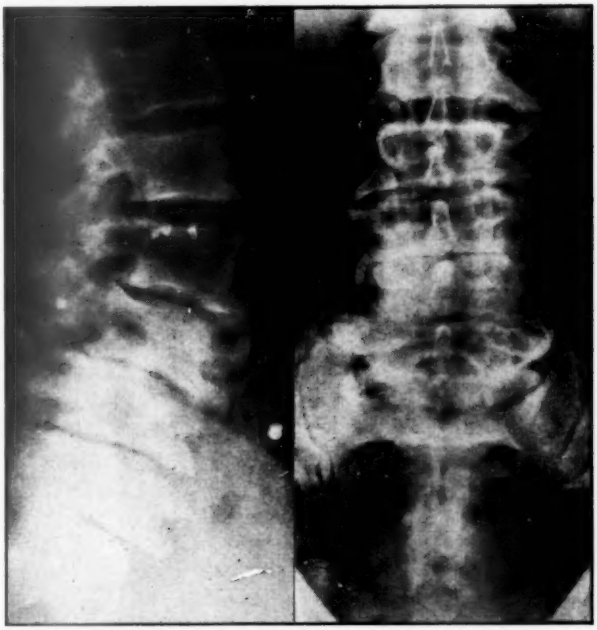


FIG. 4 (*Case I*).—Purely hypertrophic form of tabetic arthropathy: Note the massive appearance of the affected vertebræ, broad osteophytes and severe loss of disc spacing. (Reproduced by permission of the Editors of the *British Journal of Radiology*.)

Case I.—Male, aged 64, referred for X-ray examination to exclude a spinal injury after a fall. The films of the lumbar spine (Fig. 4) showed (1) Progressive enlargement of vertebræ. (2) Massive appearance of the spine. (3) Sclerosis. (4) Amorphous texture. (5) Loss of disc spaces. (6) Osteophytosis.

Subsequent enquiry elicited a history of a syphilitic infection in 1915 for which he was fully treated. Repeated blood tests since then were negative. Tabetic symptoms started in 1919, and of recent years he had complained of shooting pain in the small of the back, clearly distinct from lightning pains. The symptoms were not severe. There were well-marked signs of tabes and the blood and C.S.F. were normal.

Case II.—Female, aged 67. She gave a six years' history of lightning pains and ataxia. She also complained of a wearing pain in the right leg from the greater trochanter downwards and a similar pain on the left side. She had well-marked physical signs of tabes and deformity of the lumbar spine. The blood W.R. and Kahn were positive. The C.S.F. was normal. The films showed (Fig. 5): (1) Involvement of D.12 and L.1 and L.2. (2) Deformity of the spine. (3) Some bone destruction. (4) New bone formation. (5) Irregular appearance. (6) Beaky osteophyte arising from L.2. (7) Suggestion of loose bone.

Case III.—Female, aged 45, who gave a six years' history of tabes. The presenting symptoms which brought her to hospital were backache and tenderness of the lumbar spine. She had widespread signs of tabes. The blood W.R. and Kahn were positive and the C.S.F. was abnormal. There was kyphoscoliosis and abnormal spinal mobility. The films showed (Fig. 6): (1) Changes from L.1 to L.4. (2) Maximal change at L.3. (3) Severe deformity. (4) Marked bone destruction. (5) Vertebral wedging. (6) Subluxation. (7) Loss of disc space. (8) Osteophytosis. (9) New bone formation. (10) Loose bone.

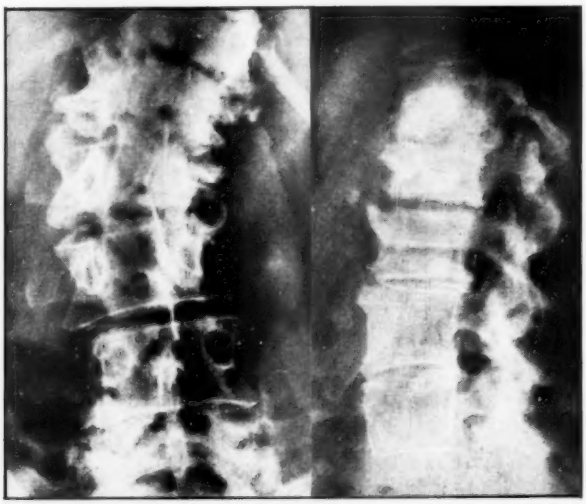


FIG. 5 (*Case II*).—Mixed destructive form of the disease; new bone formation is also present and there is suggestion of paravertebral calcification.

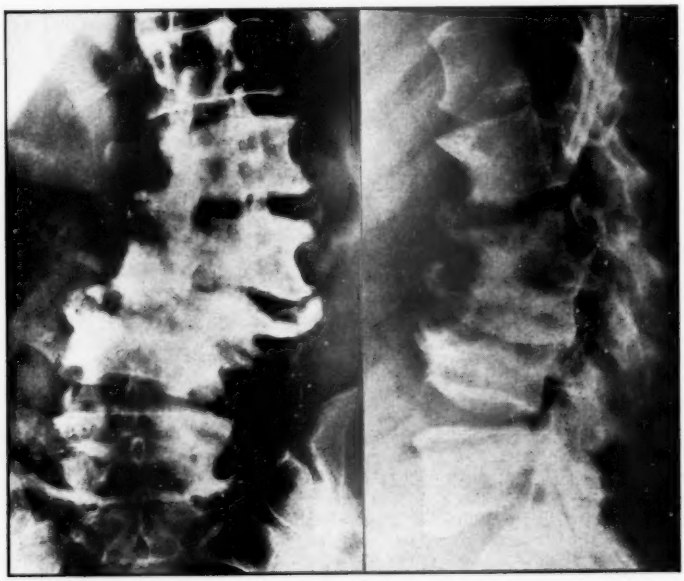


FIG. 6 (*Case III*).—Severe destructive form of the disease essentially similar to Case II.

Case IV.—Male, aged 42, with a long history of tabes and severe lightning pains. He had a past history of a spinal injury. The films showed (Fig. 7): (1) Grotesque appearance of L.4, L.5 and to a lesser extent L.3. (2) The disc space between L.4 and L.5 is practically obliterated. (3) The L.3/4 space is partly preserved. (4) Evidence of new bone formation of L.4. (5) Sclerosis and subluxation.

Diagnosis: Arthropathy superimposed on an old injury.

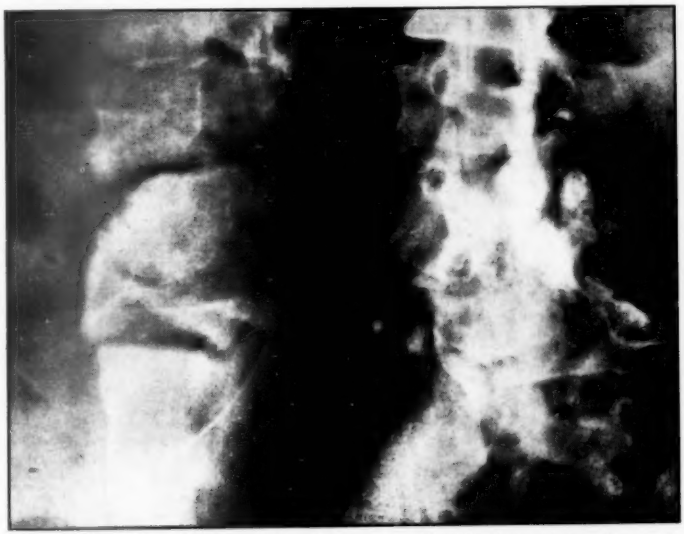
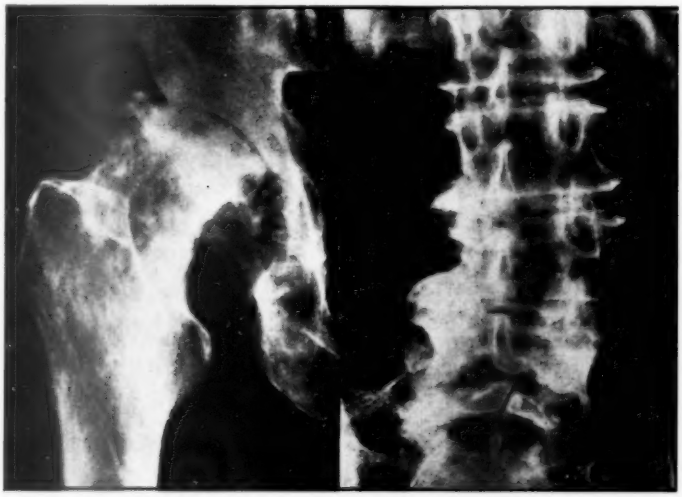


FIG. 7 (*Case IV*).—Advanced mixed form; considerable bone destruction and new bone formation with obliteration of disc space L.4/5.



A B

FIG. 8 (*Case V*).—A, typical arthropathic hip. B, massive osteophytosis of the right lateral aspects of L.3, L.4 and L.5 with loss of disc spacing; contrast with slender osteophytes along the left vertebral border. This may be an early tabetic change.

Case V.—Male, aged 52. He complained of pain in the right groin and buttock for eighteen months. An X-ray in 1951 showed marked osteoarthritic changes in both hips. He was admitted to hospital in 1952 for arthrodesis of the hips. Signs of tabes were then found and in fact his tabetic history went back fourteen years. The blood and fluid were normal. Re-examination of the hips in 1952 showed bilateral Charcot hips (Fig. 8A). A subsequent film of the spine was then taken to determine if any changes were present.

The lumbar spine (Fig. 8B) shows peculiar, massive osteophytosis of the right lateral aspects of L.3, L.4 and L.5 with loss of disc space and sclerosis. There are ordinary, slender osteophytes arising from the left lateral aspect of L.2, L.3 and L.4. The diagnosis as regards the spine is still uncertain. It is possible that this merely represents an ordinary osteoarthritis of the spine. The massive osteophytes raise the suspicion of an early arthropathy and follow-up films would be necessary.

It is apparent then that tabetic arthropathy of the spine may present a picture of its own. This is particularly true of the purely hypertrophic form of the disease. In the other varieties difficulties might be experienced in arriving at a diagnosis in the absence of a clinical history. In all cases the spine of the tabetic patient warrants special attention.

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Section of Obstetrics and Gynæcology

President—A. C. PALMER, O.B.E., F.R.C.S., F.R.C.O.G.

[*March* 27, 1953]

DISCUSSION ON PELVIC EXENTERATION

Mr. J. B. Blaikley: In 1949 I had the pleasure of assisting Professor A. Brunschwig with an anterior exenteration on one of my patients when he was in this country for the 1949 British Congress. A little later I saw him working in the Memorial Hospital, New York. It was clear to me that ultra-radical surgery for certain cases of malignant disease in the pelvis ought to be given a trial, and that the patients afterwards found life by no means intolerable. When I returned to England, Mr. Charles Read had already done two or three of these operations, and since I see a good deal of carcinoma of the cervix he encouraged me to undertake this very radical surgery also.

I will briefly describe these operations:

(1) *Anterior exenteration.*—This entails removal of the uterus, vagina, bladder and all the pelvic cellular tissue together with the iliac and obturator lymph nodes; it may be necessary to remove the whole of the vagina and even the vulva as well, but not always. The first step, usually, is to open the abdomen and confirm that it seems possible to complete the operation. Straight away both suspensory ligaments of the ovaries should be divided and the ureters as low down as is feasible, leaving a strip of peritoneum attached to them; it is then possible to identify the internal iliac arteries where they divide and ligate the anterior branches. The corresponding veins are left till later. Having done this there should be relatively little bleeding. The bladder and pelvic cellular tissue are stripped from off the pelvic walls, almost entirely by pressure of the finger-tips; the anterior tributaries of the internal iliac veins are identified and ligated towards the end of this stage. The rectum is next separated from the utero-sacral ligaments by gauze pressure and a minimum of cutting. Next all the cellular tissue is freed from the upper surface of the levatores ani and it is then possible to divide the vagina at the level of the pelvic floor if the growth does not extend below the upper one-third of the vagina; but if it extends below this, then a perineal dissection must be done and the whole mass removed from below.

I anastomose the ureters into the upper few inches of the sigmoid colon using the simple direct anastomosis used by Brunschwig. The ureters are anchored mainly by suturing the attached peritoneum to the wall of the bowel.

An anterior exenteration is applicable to growths of the cervix involving the bladder or ureters, growths of the anterior wall of the vagina, and growths of the urethra; also I believe genito-urinary surgeons sometimes use it in cases of carcinoma of the bladder.

(2) *Total exenteration.*—This operation entails removal of the rectum and most of the sigmoid colon in addition to the rest of the pelvic contents, and the patient is left with a wet colostomy, which is best made at the umbilicus after this structure has been excised.

Total exenteration is necessary if the rectum is invaded by growth as well as the bladder; such growths have usually arisen in the cervix.

(3) *Posterior exenteration.*—This is really an abdomino-perineal resection of bowel, together with removal of the uterus and vagina, and maybe vulva. The ureters and bladder are left intact. The clearance of pelvic cellular tissue is necessarily less complete than in the first two operations.

Posterior exenteration is applicable to growths of the cervix invading the rectum and growths of the posterior vaginal wall.

All three operations can be abdominal procedures only, or combined abdominal and perineal operations, according to the site of the cancer. I have tried a synchronous combined operation, but because of the often difficult dissection of the perineum, which is not possible except in the full lithotomy position, I do not believe this modification is satisfactory; the perineal operator is too handicapped.

The 15 operations I report have given me some fairly clear ideas on when to undertake an exenteration and on the risks involved. I set out with the idea that I would only advise such operations when radiotherapy had failed or was not applicable. As a result of three years' experience I still think this is the right attitude.

Most of the time one finds one is considering advanced cases of carcinoma of the cervix, but the results of radiotherapy in good centres are so good, as shown by the Scandinavian figures (Table I), even in Stage II and Stage III cases, that one must, I am convinced, give radiotherapy as the primary treatment. Our own results at the joint Chelsea-Royal Cancer Hospitals Centre (Blaikley, Lederman and Lewis, 1952) are comparable, in the small number of cases treated in 1944, 1945 and 1946 and this makes me feel this way in respect of the patients I see.

TABLE I.—RESULTS OF RADIOTHERAPY IN CARCINOMA OF THE CERVIX

	Number of cases treated	Alive without evidence of disease	Relative five-year cure rate %
Stage I	919	591	64·3
Stage II	2,169	1,064	49·1
Stage III	1,665	434	26·1
Stage IV	533	54	10·1
Total	5,286	2,143	40·5

106 cases were not treated, usually because the disease was altogether too advanced.

The absolute cure rate therefore is 39·7%.

The above table is compiled from the League of Nations Annual Report on the Results of Radiotherapy in Cancer of the Uterine Cervix, the Fifth Volume. The table refers to those patients treated at the 7 Scandinavian Centres during the years 1936–41.

Table II gives summaries of the case histories of my 15 cases, and of the treatment they had received initially. (Several were referred from *other* surgeons with a view to possible exenteration.) It will be seen that diseases other than carcinoma of the cervix, especially carcinoma of the vagina, figure quite prominently. Carcinoma of the vagina does not respond very readily, but none the less I would ordinarily give radiotherapy in the first place. Carcinoma of the urethra may well be best treated by anterior exenteration as the primary treatment in my opinion.

Fig. 1 shows the specimen from Case 11.

FIG. 1 (Case 11).—Carcinoma of vagina invading bladder.

Table III shows my results.

TABLE III.—RESULTS OF EXENTERATIONS

	Number	Alive	Dead
Anterior	12*	4*	8
Posterior	1	1	0
Total exent. ..	2	1	1
Total	15*	6*	9

* One was probably not malignant. 4 died as a direct result of the operation.

TABLE II.—PELVIC EXENTERATIONS, 1950, 1951, 1952

Name and age	Disease	Previous radiotherapy	Previous surgery	Date and type of exenteration	Condition March 1953	Lived
1. Mrs. Ch. 34	Carcinoma of cervix. Stage II	December 1949 Stockholm Radium, full. No D.X.T.	—	February 1950 Anterior	Alive and well. No sign of disease	3 yrs. 1 mth.
2. Mrs. Lo. 70	Carcinoma of cervix. Recurrent, with vesico-vaginal fistula	1929	—	October 1950 Anterior	Dead	—
3. Mrs. Sc. 60	Carcinoma of cervix. Stage II	May 1950	—	November 1950 Total	Dead	—
4. Miss Be. 54	Carcinoma of vagina invading bladder	November 1950 Stockholm Radium, 1 dose	—	December 1950 Anterior	Alive and well. No sign of disease	2 yrs. 3 mths.
5. Mrs. Pe. 60	Carcinoma of cervix. Stage IV. Recurrence in lower vagina	March 1950 Stockholm Radium full. D.X.T.	April 1951 Inguinal and iliac lymph-adenectomy	April 1951 Anterior	Dead	9 mths.
6. Mrs. Bo. 55	Carcinoma of cervix. Stage IV. Vesico-vaginal fistula	April 1951 D.X.T.	—	May 1951 Anterior	Dead	½ mth.
7. Mrs. Gr. 43	Carcinoma of cervix. Stage II.	May 1951 Stockholm Radium, full. D.X.T.	—	July 1951 Anterior	Dead	4 mths.
8. Mrs. Hu. 50	Carcinoma of cervix. Recurrent, invading bladder and rectum	October 1950 Vaginal radium for recurrence	Dec. 1949 Wertheim. January 1950 Ureter re-implanted for fistula	July 1951 Total	Alive and well. No sign of disease	1 yr. 8 mths.
9. Mrs. Ga. 71	Ca. of pelvic colon, invading uterus and rectum. Large secondary in post. wall vagina	—	—	October 1951 Posterior	Alive and well. No sign of disease	1 yr. 5 mths.
10. Mrs. Ja. 63	Carcinoma of cervix. Stage I. Recurrent, invading bladder and vagina	Sept. 1950 Stockholm Radium, full. D.X.T.	Dec. 1950 Iliac lymph-adenectomy	October 1951 Anterior	Dead	—
11. Mrs. Ho. 65	Carcinoma of vagina. Recurrent invading bladder	June 1951	Sept. 1951 Inguinal lymph-adenectomy	October 1951 Anterior	Alive. No sign of disease	1 yr. 5 mths.
12. Mrs. He. 41	? chr. abscess. ? sarcoma invading bladder and uterus	—	—	June 1952 Anterior	Alive. No sign of disease	9 mths.
13. Mrs. Ke. 38	Carcinoma of cervix. Stage II	D.X.T. Jan. 1952	—	February 1952 Anterior	Dead	5 mths.
14. Mrs. Ri. 59	Carcinoma of urethra	—	Inguinal lymph-adenectomy	July 1952	Dead	4 mths.
15. Mrs. Ew. 60	Carcinoma of cervix. Stage II	January 1952 Stockholm Radium, full. D.X.T.	—	October 1952 Anterior	Dead	2 mths.

Table IV shows complications and causes of death.

TABLE IV.—COMPLICATIONS AND CAUSES OF DEATH

Name	Age	Removal	Complications		Death from
1. Mrs. Ch.	34	Satis.	None	A	—
2. Mrs. Lo.	70	Satis.	—	D	Hæmorrhage and shock. Lived 1½ hours
3. Mrs. Sc.	60	Satis.	—	D	Circulatory failure. Lived 3 days
4. Miss Be.	54	Satis.	10 weeks later operation for prolapse of ileum through vulva	A	—
5. Mrs. Pe.	60	Unsatis.	Developed rectal fistula from necrosis of tissues	D	Recurrence of carcinoma which was adherent to ischial spine
6. Mrs. Bo.	55	Unsatis.	—	D	When apparently getting well, died suddenly from acute pulmonary œdema. ? low blood potassium
7. Mrs. Gr.	43	Satis.	—	D	Carcinomatosis
8. Mrs. Hu.	50	Satis.	Anuria for 5 days. Semi-coma from uræmia	A	—
9. Mrs. Ga.	71	Satis.	—	A	—
10. Mrs. Ja.	63	Satis.	Threatened cardiac failure	D	Pulmonary embolism
11. Mrs. Ho.	65	Satis.	6 months later: strangulated ileum, under right ureter—resection	A	—
12. Mrs. He.	41	Satis.	—	A	—
13. Mrs. Ke.	38	Satis.	Bilateral pyelonephritis. Right nephrectomy	D	Abscess in remaining kidney. Uræmia
14. Mrs. Ri.	59	Unsatis.	—	D	Recurrence
15. Mrs. Ew.	60	Unsatis.	—	D	Cardiac failure after 6 weeks. Inanition

What have I learnt from these 15 cases?

(1) It is sometimes not possible to say whether a mass is fixed until examination is made under anæsthesia or even an exploratory laparotomy is done.

(2) If it is necessary to do a perineal dissection as well as an abdominal operation, it is a great advantage to do the perineal part first. This avoids a great deal of shock.

(3) If there is doubt about the response of a carcinoma to radium, D.X.T. to the pelvic walls should be delayed if possible until the decision qua operation is made.

(4) It is possible to strip the cardinal ligaments and uterosacrals off the pelvic walls in their entirety and to wipe the rectum off these ligaments with a gauze swab. It is during this stage that the internal iliac veins are best ligated, although the arteries are tied at the very outset.

(5) The post-operative course is unpredictable: unlikely cases get on well, others where success seemed probable die in the first few days. The kidneys are all important to success, but the most difficult thing to assess beforehand is the renal function; even though the blood urea is normal and the ordinary kidney tests are satisfactory there is often sufficient renal impairment to lead to failure after operation. This may be first shown by an intractable acidosis, even though secretion seems to have got satisfactorily under way.

I believe that if there is any degree of bilateral ureteric obstruction the outlook is poor. If one kidney is absolutely normal, however, even though the other is not secreting, the outlook is sufficiently good to justify operation.

(6) For the assessment of renal function and the control of the blood electrolytes afterwards I am much indebted to Dr. W. H. H. Merivale. I believe it is of the greatest value to keep a check on blood potassium, sodium, chlorides and bicarbonates, and not to rely on guesswork. It is usual to have a period of anuria after the operation lasting one to three days, and during this time not only may the blood potassium rise dangerously high or sink dangerously low, but, as I have just said, extreme disturbance of the balance between chlorides and bicarbonates can be fatal.

(7) There is a very great difference in the severity of the operations of anterior and total exenteration and that of posterior exenteration, because division of the ureters adds very greatly to the risk, not so much at the time but in the immediate post-operative period. It might appear wise to make the operation a two-stage one and implant one or both ureters into the colon a fortnight before doing the excision, but this does not work. There is too much cellulitis at the second operation to enable one to find the tissue planes and isolate the vessels clearly.

Jacobs (1952) gives his results for this operation of ureteric intestinal anastomosis in vesico-vaginal fistula. It shows that 7 women out of 22 died soon after operation.

There seems to be a general consensus of opinion that a ureter should be put into the colon with the minimum of suturing, and my own practice has followed that of Brunschwig. I put the ureter straight in through a stab wound, anchor it with a terminal stitch transfixing the wall of the bowel, perhaps a stitch on either side, and then anchor it further with the flap of peritoneum which is left attached to the ureter when it is first isolated and divided. A tube is, of course, left in the rectum for five to seven days.

Jacobs stresses that afterwards the patient should empty the bowel at intervals of two to three hours during the day, and at least once at night to avoid aggravation of any tendency to chronic acidosis.

(8) All these patients need a lot of blood. Even though only two pints are transfused at the time of operation, inevitably another three or four pints are required within the next few days as the hæmoglobin estimations show a rapid fall in the post-operative period to very low figures.

(9) The patient must have considerable courage and stamina, and must have a good incentive to live.

Summary.—It is too early to assess the long-term results, but it does seem probable that in some cases where carcinoma has remained localized to the pelvis it is possible to eradicate it by ultra-radical surgery. The prognosis after transplantation of the ureters into the colon according to the experience of urologists is variable, some degree of stricture at the site of anastomosis is common, and sometimes progressive destruction of renal function by back pressure and infection leads to death in a year or two; others live twenty years.

I am satisfied that exenterations have a place in the treatment of recurrent carcinoma of the cervix and very occasionally as a primary treatment for this and other forms of carcinoma of the pelvic organs. I am not very happy about total exenterations. Anterior exenterations can be very satisfactory once the anal sphincter has developed good tone, though there is a tendency to incontinence at night.

It may be asked whether in some of these cases it might not be as satisfactory to do a Wertheim's hysterectomy. In my experience the results of this operation when undertaken for recurrent carcinoma of the cervix after radiotherapy are very poor and it is seldom, if ever, the proper thing to do. Finally I would emphasize that there is no comparison between an anterior exenteration and a Wertheim's hysterectomy as regards the satisfactory clearance of pelvic cellular tissue and lymph nodes.

Only time will show the complete picture, but even those that die early are often spared a great deal of unpleasant bleeding, discharge, and pain.

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Mr. Stanley Way: By pelvic exenteration I mean the removal of the uterus, bladder and rectum *en bloc*. I have removed the uterus and bladder and the uterus and rectum on many occasions—and I have one six-year survivor in this group—but I do not consider these lesser operations to be pelvic exenteration.

Apart from radiotherapy and surgery there is at the moment no way of treating these patients. A patient with pelvic cancer if left untreated will assuredly die of the disease provided that she is not carried off by something else first. This seems to me to be the chief reason for holding this discussion which I think, as far as this country is concerned, is premature, since the operation is only just beginning here and will remain experimental for a long time to come.

A perusal of WHO Annual Report on the Results of Radiotherapy in Cancer of the Uterine Cervix shows that five-year survivals of 59% in Stage I, 40% in Stage II, 22% in Stage III and 6% in Stage IV may be expected with radiotherapy (1952) and thus the more advanced the tumour, the less chance there is of cure with radiotherapy.

Dr. A. Glucksmann of Strangeways Research Laboratory, Cambridge, and I, have, for the past six years, been studying, among other things, the response of tumours of the cervix to irradiation by the study of biopsies during radium treatment. Table I shows the percentage of favourably responding

TABLE I.—RADIATION RESPONSE IN CARCINOMA OF THE CERVIX BASED ON SERIAL BIOPSIES
Newcastle Regional Cancer Organization

			1947–51		Actual survival with radium only
Stage	Favourable	Unfavourable	Total	% favourable	1940–45
I	85	77	162	53	51%
II	63	201	264	24	26%
III	2	57	59	4	8%
IV	0	30	30	0	0%
	150	365	515	30	24%

cases which we have found in the four stages and on the extreme right of the table is the five-year cure rate which we achieved with radium alone in the preceding period and it will be seen how well they agree. Certainly we tend to stage up rather than down. Elastic thickening, for instance, which may be found in the pelvis of many women without cancer, is always ignored, and we call a good many cases Stages I and II that others might call II and III.

Our work has led me to the following conclusions: Stage I carcinoma of the cervix is (except on very few occasions where technical considerations prevent it) a radiotherapeutic problem, and the role of surgery in this stage is one of assisting in the salvage by node dissection, and by radical hysterectomy in the case which is not responding. I would utterly condemn those who only choose Stage I cases upon which to operate.

In Stage II, which is a very large group, I prefer to limit radical surgery to those cases which do not respond, but since they are many I would not quarrel with those who choose to operate on all Stage II cases. Stages III and IV cases I regard primarily as surgical problems until proved otherwise.

The role of radiotherapy in this group should be either as a preliminary to operation, to clean up the tumour or as a palliative in those cases where surgery is not feasible.

It follows, therefore, that some form of surgery more extensive than the Bonney-Wertheim operation will be necessary in many of the Stage III cases and in all the Stage IV cases. On this basis I am prepared to accept the necessity for pelvic exenteration in advanced cervical cancer. Furthermore I will accept it as a possibly more hopeful method of treating vaginal cancer.

This disease gives the most disappointing results with radiotherapy, and the usual form of surgical removal of the vagina which avoids wounding the bladder and the rectum generally leads to recurrence, whilst if the removal is wide enough to be certain of curing the tumour it will assuredly wound the rectum or the bladder or both. I would agree with Kaiser (1952) who in a recent paper in *Cancer* said "it is because the salvage of this disease is so nearly nil that pelvic exenteration with its attendant high mortality can be considered".

In our series of exenterations there were 21 cases of carcinoma of the cervix and 1 case of carcinoma of the cervical stump of which 15 received pre-operative radium treatment. There were 5 cases of carcinoma of the cervix recurrent after radium, 2 of carcinoma of the vagina and 1 each of recurrent carcinoma of the ovary, recurrent carcinoma of the corpus uteri, and carcinoma of the vulva.

It may be suggested that the high incidence of node involvement seen in advanced pelvic malignant disease should rule out the operation at once and in support of this Table II shows the results of

TABLE II.—INFLUENCE OF NODE INVOLVEMENT ON SURVIVAL IN CASES TREATED SURGICALLY AFTER FAILURE TO RESPOND TO RADIOTHERAPY

1947 AND 1948

Clinical Stages I and II	
Total cases treated surgically after unfavourable response to radium	35
Alive and well 4½–6 years	16 (45%)
Node involved cases	
Total	19
Alive and well 4½–6 years	5 (26%)
Node free cases	
Total	16
Alive and well 4½–6 years	11 (68%)

surgical treatment of cases of carcinoma of the cervix in Stage I and II which were responding unfavourably to irradiation and on whom I operated after radium more than four and a half years ago. The differences in the "node involved" and the "node not involved" cases are striking and although the series is a small one the difference of 42 ± 15·1 is statistically significant. It may be of interest to note that at the same time a series of these unfavourably responding cases consisting of 58 patients with Stage I and II tumours was treated with radium alone and the survival rate in that group is 5%.

Brunschwig and Pierce (1948) have shown that by no means all Stage IV carcinomas have nodes involved and in our series we have 11 with nodes involved, 16 with nodes not involved and in 2 they were not removed. If the aortic nodes are involved I do not proceed to exenteration unless the patient has or is threatened with the development of a fistula. Surgical dissection likely to cure a patient with nodes in this region of the body is impossible.

Sciatic pain is an absolute contra-indication to operation since it is due to invasion of the perineural lymphatics of the lumbosacral plexus and is always associated with considerable node involvement. Remote metastases are another reason for not considering the operation, unless it be as a palliative.

One can never be really certain, even at laparotomy, that it is worth while proceeding, but from our studies with Dr. Glucksmann we have learned to distinguish certain things about a carcinoma of the cervix which are unfavourable and certain things which are favourable and I have devised a prognostic scheme which takes no account of the extent of the local tumour into consideration, and

which is applicable to cases which have first been treated by radium and then had the abdomens opened. Table III shows those points and the importance which we attach to them. If the tumours

TABLE III.—NEWCASTLE METHOD OF CALCULATING SURVIVAL BASED ON PATHOLOGICAL FINDINGS DURING RADIATION TREATMENT AND AT LAPAROTOMY

Favourable response to radiation (based on serial biopsies)	+2
Unfavourable response to radiation	−2
Lymphatic emboli present in pre-treatment biopsy	−1
Lymphatic emboli not present in pre-treatment biopsy	0
No nodes involved at laparotomy (based on node smear at operation)	+4
Nodes involved at laparotomy (favourable response group)	−1
Nodes involved at laparotomy (unfavourable response group)	−2
Bilateral node involvement (irrespective of response)	−2
Group B nodes involved (common iliac)	−4
Group C nodes involved (aortic)	−5

respond favourably to radium then 2 points are allotted on the credit side, but if it is unfavourable then 2 are deducted. If lymphatic emboli are seen in the initial biopsy we deduct another point since nearly 70% of this group have involved nodes. In those in whom emboli are not seen the node involvement is less than half this figure, but since their absence may be due to taking the biopsy from the wrong place or taking too small a biopsy we do not add points if they are absent.

The facts mentioned so far can be deduced before the abdomen is opened. When it is opened we can assess the node involvement. Clinically, of course, this is most unreliable except when huge fixed nodes are found, so we take out any suspicious nodes and one from each aortic group (which if involved would rule out the operation) and we submit them to a smear examination by the technique devised by my assistant Miss Dearing.

The answer can be supplied to the surgeon within six minutes of removing the node. Miss Dearing (1952) published this technique last year and has now studied over 500 lymph nodes in this fashion with an accuracy of 98%. This gives us a fairly comprehensive study of the state of the nodes in the operating theatre. If the primary tumour has responded favourably to radium we have found that node involvement, when it is present, is not so formidable as when the tumour responds unfavourably but in the case of bilateral node involvement it makes no difference how the primary tumour has responded. The farther away from the tumour involved nodes are found the more serious is the prognosis. Since all patients start this scheme with zero it follows that the most they can get on the credit side is 6 but they may be bad enough to get 19 on the debit side. After I had worked out this points system I fitted it to 187 cases of carcinoma of the cervix that I had treated more than three years ago and it worked out remarkably well as can be seen from Table IV. In the −19 to −14 groups

TABLE IV.—ACTUAL THREE-YEAR SURVIVAL RATE FOR 187 CASES TREATED MORE THAN THREE YEARS AGO, BASED ON NEWCASTLE METHOD

Total cases treated by radium and subsequently subjected to laparotomy, 187
(Operative procedures include simple laparotomy, node dissection, radical hysterectomy and exenteration)

Three-year survival rate for entire group, 45·4%

	−19 to −17	−16 to −14	−13 to −10	−9 to −7	−6 to −4	−3 to 0	+1 to +3	+4 to +6
Alive	0	0	2	7	7	10	26	33
Dead	3	13	21	23	8	16	15	3*

*Deaths from radium necrosis. No recurrence seen at autopsy.

no one survives at three years out of 16 cases, whilst in the +4 to +6 group no one has died of cancer, the only deaths in this group being due to stenosis of the ureters from radium necrosis.

Graphically it is quite impressive as can be seen (Graph 1); the −6 to −4 group is small and probably accounts for the discrepancy in the chart at that point. It is interesting to note that only one Stage IV case appeared in the −19 to −14 group, one other was in Stage III and the remaining 14 were in Stages I and II. On the other hand our longest surviving pelvic exenteration, despite the fact that she had a Stage IV tumour was in the +1 to +3 group of whom 68% are surviving at three years. Although all our exenterations were advanced cases, when fitted into this scheme many were much more favourable according to this method of prognosis than some apparently early cases. I feel that this method tests the malignancy of the tumour and is a reliable guide as to what is likely to happen.

There is one further point that I should like to make in regard to selection, and that is again based on the work of Miss Dearing (1953) who has, over the last four years, made an extensive study of the urinary tract in more than 400 cases of carcinoma of the cervix which have been admitted to my

unit. She has found that where an abnormal pyelogram exists before treatment 95% of these patients die before three years irrespective of any form of treatment except pelvic exenteration and regardless of the stage of the tumour. Although the highest percentage of cases with an abnormal pyelogram is found in Stage IV nevertheless 11% of Stage I cases and 24% of Stage II cases have an abnormal pyelogram on admission. Since we have returned some of these kidneys to normal by pelvic exenteration I believe that this should be considered in all cases with abnormal urograms even though the stage of the disease does not otherwise suggest such radical surgery.

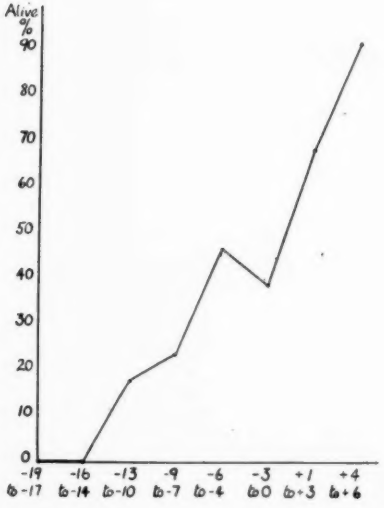
There have been 33 total exenterations performed in my clinic. 32 have been done by me and one was done by Dr. Brunschwig. Of the 32, 15 failed to leave hospital alive and Table V shows when they died and why they died.

TABLE V.—PELVIC EXENTERATION DEATHS IN HOSPITAL

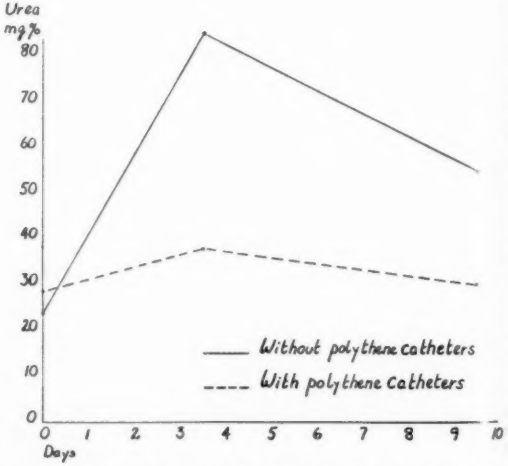
	Death on post-operative day	Cause of death
1	4th	Paralytic ileus
2	17th	Uræmia
3	3rd	Hæmorrhage
4	3rd	Hæmorrhage
5	10th	Crush syndrome
6	42nd	Pyæmia (*B. proteus*)
7	27th	Uræmia
8	4th	Pyelonephritis (*B. proteus*)
9	26th	Perinephric abscess (*B. proteus*)
10	0	Hæmorrhage
11	9th	Pyelonephritis
12	0	Hæmorrhage
13	7th	No cause found
14	8th	Bronchopneumonia
15	17th	Vena cava thrombosis

17 recovered from the operation and 9 have subsequently died as shown in Table VI. I have thought it wise to include a statement of their condition from the time of operation until death.

8 are surviving (Table VII) one of whom is still in hospital doing very well. They are all excellent except 2 who are having slight difficulty with their bags at the moment. This we expect until the patients get thoroughly accustomed to handling them. For this reason alone a patient must be so dumb that she can be taught parrot fashion what to do, or she must have a reasonable amount of intelligence. This is a very important point in the selection of patients for this operation and it is one which can only be learned by experience.



GRAPH 1.—Three-year survival rate according to Newcastle prognostic method, 187 cases.



GRAPH 2.—Average blood urea levels after operation with and without polythene ureteric catheters.

TABLE VI.—PELVIC EXENTERATION

REMOTE DEATHS

	Time after operation	Cause of death	Condition in interim
1	1 year 1 month	Recurrent carcinoma	Good for 6 months. Physically miserable for 7 months
2	2 years 9 months	Intestinal obstruction. No recurrence	Physically well for 2 yrs. and 6 months. Mentally miserable all the time
3	9 months	Intestinal obstruction due to metastatic carcinoma	Excellent until 3 days before death
4	2 years 3 months	Pulmonary embolus following closure of fæcal fistula	Good for 1 year 9 months. Poor for 6 months
5	5 months	Recurrent carcinoma	Well. Extremely low I.Q.
6	1 year 3 months	Metastatic carcinoma	Good apart from trouble with a drunken husband
7	1 year 1 month	Pyelonephritis	Excellent right up to death
8	3 months	Multiple skin metastases	Good
*9	8 months	? intestinal obstruction ? due to metastases	Excellent

* No autopsy.

TABLE VII.—PELVIC EXENTERATION

SURVIVING CASES

1	3 years 9 months	Excellent
2	1 year 9 months	Excellent
3	1 year 2 months	Excellent
4	6 months	Excellent
5	4 months	Good
6	3 months	Excellent
7	2 months	Excellent
8	2 months	Good

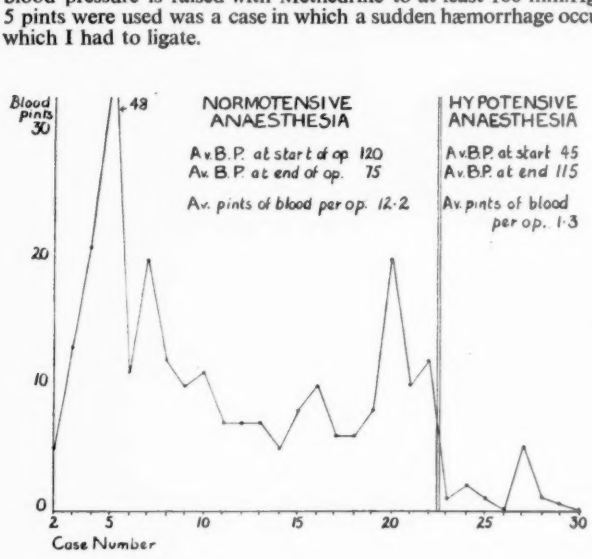
This operative mortality of 45% is far from satisfactory. I had been impressed by Brunschwig's use of polythene for skin ureterostomies which I had seen in New York in 1951 and so I got Messrs. Down Bros. to make to my design a polythene ureteric straight catheter; the upper end is bevelled so that it will not damage the ureter when it is inserted. One end is passed up the ureter into the renal pelvis and the other is brought out through the colostomy and inserted into the colostomy bag. I leave them in for about ten days and usually longer. They keep the wound dry from the start and the urine usually remains sterile. They do not get foul and have little tendency to block and we have had no post-operative anuria. Graph 2 shows the average post-operative blood ureas on the fourth day and the tenth day of a group of cases with polythene tubes and a group without. It is now quite unusual in my unit for any form of ureteric transplant to get either anuria or a rise of blood urea greater than 10 mg.% after operation.

When Dr. George Donaldson, Senior Anæsthetist to the Queen Elizabeth Hospital, Gateshead, where my unit is situated, took up hypotensive anæsthesia, we began to make real progress. Prior to that we had attempted to keep the blood pressure at 100 mm.Hg during operation by liberal transfusion using the pressure transfusion apparatus invented and given to us by Dr. Virginia Pierce of the Memorial Hospital, New York. Even then we often failed to keep the pressure up. Graph 3 shows the amount of blood which we gave to each case during the operation and in the immediate post-operative phase. The record for the first case is not included as it was lost when my unit was moved to the Queen Elizabeth Hospital in 1949. I think that she had 13 pints in all. One patient received a transfusion of 48 pints which lasted for three days until the patient died. At autopsy we found that the bleeding was coming from the vertebral veins where the aortic nodes had been dissected and that the blood had accumulated under the peritoneum in the upper abdomen and not run into the pelvis.

At this early stage I had considered that if a patient was Rh negative she could not be considered for operation but we did one through the courtesy of Dr. Sheila Murray, the Director of the Newcastle Regional Transfusion Service, to whose help and sympathetic understanding of the experimental nature of our early work I would like to pay a tribute.

Of all the various methods of producing hypotension—hexamethonium as used by Brunschwig, the total spinal method of Gillies as used by Meigs and arterial and venous bleeding—I have been most impressed from what I saw elsewhere with the total spinal technique, and this is what we use.

Dr. Donaldson has used it for all our major cancer surgery for the last eight months with great success. We have performed eight total exenterations on a total for all cases of 9½ pints of blood and we have had 2 deaths in that group whereas we had 12 in the previous 23 (Graph 3). The lack of bleeding in these cases is really remarkable and whilst the transplant, which I do last, is being performed the blood pressure is raised with Methedrine to at least 100 mm.Hg. The one case in this group where 5 pints were used was a case in which a sudden hæmorrhage occurred from a wound of the vena cava which I had to ligate.



GRAPH 3.—Transfusion in pelvic exenteration — normotensive and hypertensive anæsthesia.

If there is any extenuating circumstance in our high mortality I would say that it is the general nature of the material which we handle. The North East of England was, from 1930, a depressed area and such good protein as a family obtained usually went on the men and the children. When the depression lifted rationing came in and so we now have a set of women who have been starved of first-class protein for over twenty years. We have difficulty in getting them to take a high protein diet for a fortnight before operation and in our experience this operation is always followed the next day by a large drop in the serum protein. If the protein is low to start with this can be very serious. In our early cases we failed to realize this and to do anything about it, and we operated on a number of patients whom we should now regard as improperly prepared for operation.

Those five years have been very depressing ones but I should like to thank Dr. Brunschwig and his assistant Dr. Pierce for the great help and encouragement that they have given me personally and by correspondence.

I cannot tell what ultimate place it has in the treatment of advanced pelvic cancer but I am sure that it has a place and that it has come to stay as long as surgery and radiotherapy are the only means of treating this disease. It is a formidable operation, not so much from the technical point of view, as from the choice of case, the preliminary preparation and the after-care. All of our cases are told that if they have any worries they can come to the unit at any time and discuss them. They do and we find this gives them great confidence and finally their visits become less frequent.

This is not an operation which can be done by anyone who has not had considerable experience of malignant disease and of pelvic surgery as a whole, and I would advocate its limitation to those surgeons who handle a lot of this type of material.

Perhaps I may close by quoting from a manuscript which Dr. Joe Meigs (1953) sent to me: "This operation is definitely experimental and should only be done by those who are purposely seeking to achieve the best means of doing it . . . and the occasional performance of operations for cancer of the cervix can only be condemned."

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Mr. Charles D. Read: The cases I have to record are of little statistical significance, as the series is too small—indeed I believe that in this country there is no series to date which is statistically significant.

The only possible justification for operations of this magnitude is the prospect of salvaging a few patients who are otherwise doomed—it is a desperate measure for a desperate condition—and generally the alternative to the operation of pelvic exenteration is death. I have never held palliative exenteration to be a justifiable procedure and have performed it only in cases where there would appear to have been a prospect—even remote—of cure.

In 1948 I saw Brunschwig in the Memorial Hospital in New York perform some of his earlier operations at a time when he was embarking on his first series of 100 unselected cases. Some of these offered a prospect of cure, but many also were performed for palliation only. His original concept of the possibilities of exenteration was based on the reports that careful autopsies on patients dying of advanced cancer of the pelvic organs showed that in over 30% of cases the patient died with the disease still localized to the pelvis. In a recent paper by Cosbie of Toronto in the *American Journal of Obstetrics and Gynecology* it is reported that in post-mortem examinations of 27 patients dying of advanced pelvic cancer 17 showed remote metastases. Morris and Meigs in an article in *Surgery, Gynæcology & Obstetrics* showed an almost identical figure.

The problem then is, can any of these patients with active advanced uncontrolled cancer, but with the disease still localized to the pelvis, be saved?

The difficulty immediately arises in that it is not possible with certainty to know that the disease is so localized. A careful clinical examination must be performed and X-rays of chest, long bones, spine and pelvis should show the absence of secondary deposits, but even then some patients must harbour metastases which are demonstrable neither clinically nor radiologically.

Even if the disease be still localized to the pelvis the general condition of the patient may make the exenteration inadvisable. Extreme adiposity, cardiac and renal disease are the three main obstacles in respect of this. The local condition is occasionally so advanced that complete removal is impossible, and I have never been successful in exenterating a patient with what the Americans call a "frozen pelvis".

Renal efficiency must be reasonably good as evidenced by blood urea estimation and intravenous urography, though in three instances patients have been successfully exenterated with one non-functioning kidney. One such patient lived for twenty-four months in comfort.

In general I have not performed the operation unless the following conditions have been fulfilled.

(1) Advanced pelvic cancer uncontrolled by irradiation. (Exceptions to irradiation are advanced primary carcinoma of ovary, vulva, rectum and bladder.)

(2) Disease localized to pelvis—clinical and X-ray evidence.

(3) Reasonable renal efficiency. (Blood urea and intravenous urography.)

(4) Patient's general condition is such that she may reasonably be expected to survive the operation.

Partial or Complete Exenteration

From the patient's point of view the anterior exenteration is infinitely preferable, but its scope is limited to those cases of cancer of the cervix in which the bladder alone is also involved and in which there is conclusive evidence that posterior extension is absent. In addition, patients with carcinoma of the urethra involving the bladder neck, and, of course, cases of primary carcinoma of the bladder are suitable. In most instances, however, total exenteration is necessary, as the disease is locally far advanced. The total exenteration involves the performance of a wet colostomy, but a so-called dry colostomy with double skin ureterostomy may be an alternative. More recently, the ureters have been implanted into an isolated segment of colon which is brought out as a separate urinary exit while a colostomy of the usual type is performed. Ingenious bags have been introduced as receptacles for various urinary and fæcal exits.

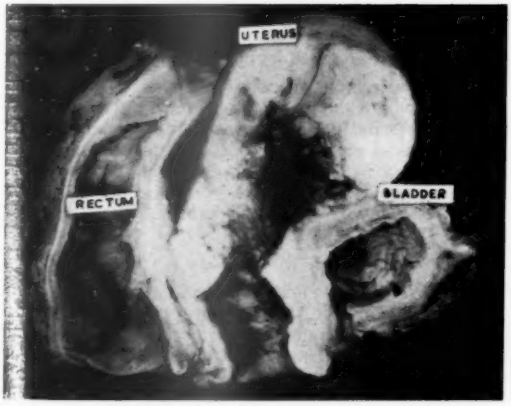

Fig. 1.—Total pelvic exenteration for advanced cancer uncontrolled by previous irradiation.

Posterior exenteration has a limited scope and, of course, does not involve any urinary deviation.

In Brunschwig's series the proportion of partial exenterations to total exenterations is roughly one to two.

Technical Points

(1) *Anæsthesia.*—In all but 2 cases anæsthesia has been induced by Pentothal—gas and oxygen sequence, with the use of a relaxant such as Tubo-curarine or Flaxedil. In 2 instances spinal anæsthesia was used, but we soon abandoned this as in each case the patient's condition deteriorated markedly at the end of the operation though both survived. I have to date avoided the use of the hypotensive drugs because, though they minimize hæmorrhage, I feel that their use might increase the incidence of thrombosis. I may be incorrect in this view.

(2) *Hæmorrhage.*—Blood loss can be minimized if immediately after abdominal exploration for operability both internal iliac arteries be doubly ligated at their origin. This is the first important step in the operation and immediately precedes low division of the ureters. After this, careful attention to hæmostasis as the operation progresses will minimize blood loss. In all cases a drip transfusion is used in the operating theatre. The size of the transfusion should aim at replacing all blood loss and on return to the ward an extra 600 ml. of blood is transfused. The smallest transfusion given in my series has been 2 pints and the largest 7 pints. The average case requires in all 3 pints of blood at operation and in the immediate post-operative phase, though subsequent "topping up" transfusions may be necessary.

(3) *Lymph nodes.*—Immediately after ligation of the internal iliac arteries and after division of the ureters a block dissection of the common, internal, and external iliac and obturator nodes is performed, and all the nodes are swept medially so that eventually, when the specimen is excised, nodes and viscera are removed *en bloc.*

(4) *Wet colostomy.*—At operation the colostomy should project about 1 in. from the abdominal skin surface. It tends to retract. If this projection is maintained it facilitates its insertion into the Rutzen, Pierce, or plastic disposable bag aperture. This maintains a healthier surrounding skin and minimizes leaks around the bag flange. I now excise the umbilicus and bring out the colostomy at this site. This allows the bag fixation to be made at a higher level on the abdominal wall with consequent increased comfort, and it ensures better bag application.

(5) *Uretero-intestinal anastomosis.*—It would appear that the simplest method of uretero-colic anastomosis is the best, because this has to be performed at the end of a sometimes long and exhausting operation. For this reason I have always preferred the short Coffey anastomosis, though on three occasions I have done a direct stab transplant. It will be seen that the uretero-colic anastomosis itself, apart from the exenteration, carries a relatively high mortality. In the report published by the British Association of Urological Surgeons in June 1952, in 2,977 ureteric transplants performed on 1,673 patients, by all methods, for all conditions, in the first four post-operative weeks 21·1% of the patients died, and in some of these the transplants had been performed alone without further operative procedures. My urological colleagues inform me that one must expect a mortality of 12% directly attributable to the ureteric transplant alone. Preston (1951) has published an operative mortality of 21% from ureteric transplants for vesico-vaginal fistula. It would appear that the advantage of a preliminary ureteric transplant, with subsequent exenteration, is outweighed by the risk subsequent to transplantation of disrupting the anastomosis during the later exenteration, and in addition the presence of adhesions from the initial transplant may make the second, and more severe, operation more difficult. I have not performed the operation in two separate stages.

(6) *Synchronous combined operation.*—I have so far not practised the simultaneous combined abdominal and vaginal approach as suggested by Howkins for the extended Wertheim operation. It obviously has advantages, but it is important that a careful examination of the abdominal cavity for metastases and operability should be concluded before the vaginal operator begins his task.

(7) *Exenteration without vulvectomy.*—It is possible to remove the whole bladder, vagina and anal canal via the abdominal route, and in all patients in whom the growth appeared to extend no lower than the upper third of the vagina I have adopted this procedure. The shock of the operation is thus minimized, as pointed out by Meigs. I have had reason to regret my decision to do this on three occasions when, once macroscopically, and twice microscopically, it was evident that my growth clearance had been incomplete. 1 such patient was an operative death while the other 2 showed recurrence of the growth, though 1 is still alive over one year after the operation.

Urinary Secretion After Operation

Two main factors influence the post-operative course so far as urinary output is concerned: *shock* with its associated anuria or oliguria and *œdema* at the site of the anastomosis with its attendant ureteric obstruction. In the absence of shock I have to date maintained intravenous glucose infusion at a slow rate until urinary secretion is established, and, in some instances, intravenous sodium sulphate solution has been spectacularly successful on the second day in producing diuresis. With the shocked patient, we have limited fluid intake to 1,200 ml. in the twenty-four-hour period, as suggested by Bull and others. I have had no experience of the use of indwelling ureteric catheters or polythene tubing in the anastomosed ureters.

Electrolyte Balance

It would appear that sodium-potassium imbalance is most important in the post-operative period, and for this reason intravenous saline should be used sparingly, as the sodium tends to displace and replace the tissue potassium. Potassium deficiency may be estimated biochemically, but it is easily detected by the relatively striking appearance of the electrocardiogram. Potassium displacement would tend to be favoured in these operations by the absorption of sodium chloride from the urine in the bowel as a result of ureteric transplantation. It would thus appear that it is more troublesome following the anterior operation than after total exenteration, as, in the latter, the urine almost immediately escapes through the wet colostomy, whereas with the intact bowel, with sphincter control, the reservoir of urine favours absorption.

Table I.—Exenteration Operations

Patient	Age	Primary site	Pre-operative irradiation	Type of operation	Date	After-history
Mrs. T.	70	Ca. Cx. recurrent	7 months previously	Anterior exenteration	23.7.49	Lived 24 months. Died recurrence ilium and uræmia
Mrs. W.	68	Ca. bladder involving vagina	None	Anterior exenteration	22.8.49	Died 3 months after operation with secondaries in liver
Mrs. B.	53	Ca. Cx. recurrent	2 years 5 months previously	Total exenteration	12.12.49	Lived 23 months. Died uræmia. No recurrence. P.M.
Mrs. H.	50	Ca. Cx. Previously attempted Wertheim. Lymphadenectomy only	Irradiation 5 months previously followed by gross pelvic sepsis	Total exenteration	26.1.50	Alive, but since exenteration has had replant of right ureter, 30.7.50, and ileo-vulval fistula closed. No recurrence
Mrs. T.	51	Ca. Cx. with extensive rectal and bladder involvement	12 months previously	Total exenteration	6.3.50	Well 4 months after operation. Untraced, lives in Persia
Mrs. W.	40	Endocervical Ca. Cx. and bladder	None	Anterior exenteration	8.9.50	Lived 9 months. Died recurrence and uræmia
Mrs. J.	56	Ca. Cx., recurrent: failed Wertheim	12 months before attempted Wertheim	Anterior exenteration	20.11.50	Alive and well
Mrs. D.	62	Ca. Cx. recurrent + Ca. ileum + ileo-vaginal fistula	12 months previously	Total exenteration + resection ileum	5.12.50	Died 10 hours: post-operative shock
Mrs. Y.	66	Ca. vagina recurrent with recto-vaginal fistula	9 months previously	Posterior exenteration	12.12.50	Alive and well
Mrs. F.	53	Ca. ovary involving uterus, bladder, and vagina	None	Total exenteration	31.1.51	Died 3rd post-operative day, peripheral circulatory failure
Mrs. L.	56	Ca. Cx.	9 months previously	Total exenteration	18.4.51	Died 9 days after operation: intestinal obstruction due to loop of ileum being strangulated between colostomy and abdominal wall
Mrs. T.	62	Ca. vulva and urethra and bladder neck	None	Total exenteration + inguinal lymph nodes	20.4.51	Alive but with recurrence
Mrs. T.	48	Ca. Cx. recurrent	13 months pre-operation	Anterior exenteration	25.6.51	Alive but with recurrence. Right posterior pelvic wall fixed to bone

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Continued from p. 765

Patient	Age	Primary site	Pre-operative irradiation	Type of operation	Date	After-history
Miss A.	49	Ca. Cx. recurrent	6 months pre-operation	Total exenteration	4.7.51	Died 23rd post-operative day. Paralytic ileus and pyelonephritis
Mrs. L.	55	Ca. Cx. recurrent	16 months pre-operation	Total exenteration	12.9.51	Recurrence in vulva: still alive
Miss C.	38	Ca. Cx. recurrent	9 months pre-operation	Total exenteration	28.11.51	Died 16 months after operation. 3 months after operation cæcovulval fistula closed. Recurrent fæcal fistula 10 months later: died after attempt to close this. No recurrence
Mrs. K.	61	Ca. vagina and rectum—fistula	12 months previously	Posterior exenteration	1.12.51	Alive and well
Mrs. C.	64	Ca. Cx. recurrent	11 months previously	Total exenteration	18.12.51	Alive and well, but foot drop
Mrs. M.	62	Ca. Cx. and vagina	X-rays only. 5 months pre-operation	Total exenteration	21.4.52	Lived 10½ months. Died of recurrence. Original operation not clear of growth
Miss M.	51	Ca. colon involving uterus and bladder	Nil	Total exenteration	25.4.52	Died 18th post-operative day. ? coronary ? embolus
Mrs. L.	38	Ca. Cx. recurrent	14 months previously	Total exenteration	30.4.52	Alive but with œdema of legs. Ileo-vulval fistula closed Jan. 1953. Probably has recurrence
Mrs. E.	37	Recurrent carcinoma following previous pan-hysterectomy for carcinoma corporis uteri	Nil	Total exenteration	6.5.52	Alive and well. Occasional recurrent pyelitis

Complications

Excluding the 5 deaths within the month immediately following the operation, post-operative complications have been many and varied.

(*a*) *Urinary leakage.*—This has occurred in 5 patients. In 3 of these, however, the leak has been a temporary one and has cleared up spontaneously by the fourteenth post-operative day. In 2 patients re-transplant of one ureter has been necessary and 1 of these is alive over three years after the initial operation. The serous seepage from the large raw area left after operation may simulate urinary leakage for a time.

(*b*) *Intestinal fistulæ.*—3 such cases have been encountered and all have occurred some months after the initial operation; in each instance there had been heavy pre-operative irradiation by radium and X-rays. 2 of the patients developed ileo-vulval fistulæ, and 1 a cæco-vulval fistula. All 3 were subsequently operated upon. For the 2 ileal fistulæ an exclusion entero-anastomosis was performed, while in the case of the cæcal fistula, excision of the offending portion of the cæcum was possible. The 2 patients with ileal fistulæ are alive and with the fistulæ closed, but while one is well three years after operation the other has a recurrence of growth. The patient with the cæcal fistula died following attempted closure of a still further fistulous track some months later. At the time of the subsequent operations all 3 patients appeared to be free of recurrence.

(*c*) *Pyelitis—pyelonephritis.*—Ascending urinary infection is by no means uncommon, but in surprisingly few cases is it severe. When it does occur, the intervals between the recurrent attacks in most instances become increasingly longer. The use of the various antibiotics can control most infections, and there is increasing evidence accumulating in America that the use of skin ureterostomies tends to diminish ascending infection. It would appear that transplant of the ureters into an isolated segment of colon, acting as a receptacle with a fistulous skin aperture, would similarly diminish the incidence of such infection.

(*d*) *Nerve injury.*—2 patients, both alive, have developed muscle weakness in one leg. In the first I purposely divided the obturator nerve in order to remove otherwise irremovable malignant obturator nodes. This is not a serious disability as the adductor magnus muscle has a double nerve supply. In the second, the patient developed foot drop and causalgic pain immediately after operation, due doubtless to unintentional intra-pelvic operative nerve trauma. The disability has persisted.

These are the main serious complications peculiar to the operation, though minor annoyances such as vulval discharge, and skin irritation around the wet colostomy, may be troublesome. After the anterior operation, complete anal sphincteric control may be defective for some considerable time.

The Future of Exenteration

I said in another place that until we can show some five-year survivals and cure, the operation is, in my opinion, on trial. Brunschwig is now in the position to show such five-year survivals, and by now has performed approximately 260 operations of partial and complete pelvic exenteration. I still am firmly convinced that the patient with distant extra-pelvic metastases should not be subjected to the operation, with the possible exception of the occasional patient, with a double vaginal fistula, if the disability is extreme, and the general condition reasonably good.

Other than in this exceptional case palliative exenteration is in my opinion unjustifiable.

At the moment it is all one can offer to a very selected group of patients who are beyond the help of less radical surgery, and who have failed to respond to radiotherapy.

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Mr. John Howkins: I shall confine my comments to four aspects of pelvic exenteration:

(1) Anæsthesia: While appreciating the advantages of operating under hypotensive anæsthesia I should like to point out that not all surgeons are satisfied with the final safety of this manœuvre, and I personally prefer the modified hypotension provided by an extradural anæsthetic, which provides most of the advantages of the total spinal without some of its more obvious dangers. The surgeon can obtain a satisfactory exposure by this means; he is not embarrassed by gut in the operative field, and the amount of hæmorrhage is minimal.

(2) I would advocate the wider adoption of the synchronous combined method of operating, with two teams, one abdominal and one vaginal, an advantage to which Mr. Charles Read has paid a generous tribute in his opening speech. By adopting this method a speedier operation with a wider dissection can be performed and in difficulty or peril the two teams can be beneficially synergistic. The great advantage of this method is that it avoids the disturbance and shock to the patient inherent in changing her position during the operation from the Trendelenburg to the lithotomy or vice versa. This alteration in position undoubtedly upsets the patient and coming at the end of a serious operation can be very shocking.

(3) Most surgeons today realize the increasing importance of frequent serial estimations of the patient's electrolyte behaviour and the prompt adjustment of any imbalance, particularly of potassium. Unless surgeons performing this major operation are alive to the possibilities of potassium deficiency, many of their patients will suffer from hypopotassæmia, from which some at least will die.

(4) On the question of the artificial bladder I want to emphasize the dangers of selective chloride absorption from the bowel in those patients in whom a bilateral ureterosigmoidostomy has been established.

Many such patients suffer from hyperchloræmic acidosis and I suggest that this absorption of chloride can be minimized by providing a separate colostomy formed from a loop of isolated sigmoid colon at the bottom of the abdominal wound into which the ureters have been implanted. This artificial bladder measures between 4 in. and 6 in. in length and provides for the collection of clean urine by a special bag. The usual colostomy in the left flank is provided for the evacuation of the bowel, which can be disciplined to behave in a regular manner, thus avoiding the constant discharge of a mixture of fæces and urine, which is always difficult to control. [He showed two illustrative slides in which such a procedure had proved satisfactory.]

Mr. G. E. Moloney: A "wet" colostomy is one of the most unpleasant of the miseries we can inflict on our patients in order to save life. It has been necessary to establish such a colostomy after pelvic evisceration, but it may not always be so in some instances. Over a year ago, in a male patient with an extensive carcinoma of the sigmoid colon invading the bladder and causing a vesicocolic fistula, I performed pelvic evisceration but left a small stump of rectum above the levator ani muscle. Then, after excising the diseased segment of bowel together with an appropriate portion of mesentery, the proximal end was brought down and anastomosed to the distal stump. The ureters were then transplanted into the colon above the anastomosis of bowel. By extensive mobilization of bowel and ligation of the inferior mesenteric artery at its origin it is possible to mobilize and approximate large gaps in the distal colon, the blood supply then coming from the transverse mesocolic artery by way of the epicolic branch. This patient made a good recovery after undergoing the complications of small intestinal obstruction and femoral thrombosis. He is at his usual work as a postman, has good anal control of urine, stools and wind, and shows no sign of recurrence. I suggest that those unfortunate women who have to suffer an excision of this nature should, whenever indications allow, have the bowel and ureters joined in this way, preferably by a one-stage procedure. I wish to compliment the opening speakers on their endeavours in this field and to join with Mr. Way in saying that this form of surgery is advanced and difficult, and such patients are best passed to a few centres and to a limited number of operators who can thus have an adequate chance to assess and develop it.

Mr. W. R. Winterton: I have done 11 exenterations in the last four years, mostly anterior but some later required a posterior. Of these, 6 are alive and 5 are dead. Those who died survived between two weeks and twelve months.

Many of these cases have been done by the synchronous combined method. This method has one grave disadvantage in the anterior exenteration, which is that by the removal of the whole vagina the anterior wall of the rectum is left exposed, and if there has been a previous course of radiotherapy there is a great danger of sloughing and fæcal fistula formation. On the other hand, the synchronous combined operation makes the separation of the rectum from the vagina easier, and this part of the operation can be extremely difficult from the loss of tissue planes.

Since most cases have had a course of radiotherapy, any attempt at conservative surgery in the pelvis as suggested by Mr. Moloney is doomed to failure through lack of blood supply. In view of the liability of the rectum to slough after radiotherapy followed by anterior exenteration, it is advisable to implant the ureters high up in the sigmoid colon so that there is sufficient bowel below it to form a colostomy without interference with the ureteric implant.

Mr. L. P. Le Quesne: Several previous speakers have mentioned the importance of the careful control of the water and electrolyte balance of patients undergoing pelvic exenteration. My own experience with these cases is limited, but in general the problems of fluid balance they present differ in no way from those associated with all major abdominal cases, and I would stress the importance of three points:

(*a*) Accurate intake and output charts are essential in the management of these problems, and in a complicated case the difficulties are greatly increased by the neglect of this simple measure.

(*b*) During the first three to four post-operative days there is a distinct risk of giving excessive quantities of intravenous fluids. The danger of overloading a patient with saline is well recognized, but it is not so clearly recognized that for twenty-four to forty-eight hours after operation there is just as much danger of overloading with water (glucose solutions).

(*c*) One of the main factors in the ætiology of post-operative potassium deficiency is a deficient intake. For this and other reasons, it is desirable to give potassium salts, either separately or together with saline, once a satisfactory urine output has developed. For some time now we have been giving a daily basic intake of 80 m.Eq. K (6 grammes KCl), at a concentration of 40 m.Eq./l, to patients on intravenous fluids, with satisfactory results. With the use of potassium solutions such as this, two precautions should be taken; first, the rate of administration should not exceed 20 m.Eq. K per hour; secondly, these solutions are potentially dangerous in the presence of oliguria or anuria, and should therefore not be given for at least twenty-four hours after operation.

Section of Surgery

President—Professor F. A. R. Stammers, C.B.E., T.D., Ch.M., F.R.C.S.

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DISCUSSION ON SURGICAL TREATMENT OF CARCINOMA OF THE PHARYNX

Sir Stanford Cade: This contribution deals solely with epithelial new growths, namely, squamous-cell carcinoma. Only lesions of the laryngopharynx will be discussed; lesions of the oropharynx and of the nasopharynx are excluded as they present quite separate problems. It is convenient to subdivide the laryngopharynx into two main parts, the epipharynx above and the hypopharynx below, the line of division being at the level of the upper border of the cricoid cartilage. As the natural history of malignant tumours of the pharynx varies with their site of origin, it is customary further to subdivide this anatomical site in four groups: (1) Tumours of the aryepiglottic fold extending to the epiglottis and arytenoid cartilages. (2) Tumours of the lateral wall of the laryngopharynx. (3) Tumours of the sinus pyriformis. (4) Tumours of the hypopharynx either on the anterior wall—post-cricoid—or posteriorly at a somewhat lower level. This subdivision is of importance, as it affects the course of the disease. The symptomatology of the lesions also differs: thus, pyriform fossa lesions are notoriously silent for a long period, the post-cricoid lesions give rise to dysphagia early, and the aryepiglottidean tumours give rise to abnormalities in the sensation of the throat. Further, the incidence of lymph-node involvement and its time of occurrence differ with the primary site (Table I).

Table I.—Lymph-node Involvement—Percentage

	+	−
Epilaryngeal	50	50
Lateral pharyngeal	63	37
Pyriform fossa	73	27
Post-cricoid	50	50

The sex incidence shows a marked preponderance in men, except in post-cricoid carcinoma, which is peculiarly a disease of women.

Diagnosis.—Early diagnosis is essential. Diagnosis should be not only of the nature of the disease, but of its exact site and, above all, its extent. It is here that diagnostic radiography is sometimes more helpful than endoscopy. A lateral view of the neck with air inflation is of greater value than the use of opaque media. Tomography also helps to delineate the extent of the disease. It goes without saying that a general examination of the patient, radiography of the chest, and blood examination should be done in all cases. Histological examination of the tumour is, of course, imperative. Biopsy is only dangerous if the piece of tissue removed does not give the pathologist a representative part of the tumour; whenever I am told: "biopsy was negative" I cannot help wishing that the patient had at that stage changed her surgeon and so perhaps ensured an earlier diagnosis. Biopsy is important not only to establish a diagnosis of cancer, but to determine its degree of malignancy, differentiation, and radiosensitivity.

We must consider such problems as the degree of operability, the likelihood of achieving prolonged control of the disease, the disabilities following operations and those after radiotherapy. The material on which I, personally, base my opinions, the sum total of my experience, covers a period of twenty-two years.

My close association with radiotherapy has brought much clinical material, and I can look back on a series of just over 400 cases of carcinoma of the pharynx which I saw and treated with my colleagues. During those twenty-two years (Table II) conventional X-ray therapy, as far as the pharynx is concerned, has been proved to be only of limited use. Radium therapy at my own hospital has proved

Table II.—Carcinoma of Pharynx 1930–1952

	Total	M	F
Epilaryngeal	77	70	7
Lateral pharyngeal	47	42	5
Pyriform fossa	167	155	12
Post-cricoid	112	30	82
Total	403	297	106

more effective, and has a place in the management of the case. As a palliative, it is of great value. Yet the pharynx is not an anatomical site where radiation can with confidence be advised as the most reliable treatment, if surgery can well deal with the lesion. It is exactly forty years since Wilfred Trotter described his lateral transthyroid pharyngotomy. In 1937—that is twenty-four years after Trotter first described it—Pilcher analysed 100 cases (including many of Trotter's own cases) treated by this method at University College Hospital; he found 7 alive out of the 100, as the result of surgical treatment alone, the longest survival being ten years, the shortest eighteen months at the time of writing.

Here are two quotations from Trotter which illustrate why he went no further than a lateral transthyroid pharyngotomy; one shows the material limitations of his times, and the second shows an attitude of mind—both of interest:

"For the surgeon, the pharynx combines three of the most formidable obstacles to the exercise of his art; it is inaccessible in a high degree, it is a seat of delicate and concentrated function, and it contains septic material to which the surrounding tissues are in no way immune."

It will be conceded that to-day sepsis can be controlled to a degree unknown to Trotter's generation; that most of us consider the pharynx as easy of access and that its function, swallowing, can be provided for by surgical reconstruction.

The second quotation illustrates his thoughts:

"I should not feel able to record as a true success the cure of a pharyngeal carcinoma won at the expense of laryngectomy."

Speaking for myself I do not consider a laryngectomy too high a price for the patient to pay for a chance of escaping death from cancer of the pharynx. Surgery is of a limited usefulness in the treatment of cancer as a whole—it is estimated that, all told, about 10 to 15% of the cancer population can be treated effectively by surgery. It is accepted that the earlier the case, the smaller the lesion, the more accessible the site, the better the results of surgery. In the case of the pharynx, it is inevitable to have to discard as unsuitable for surgical excision the majority of cases for one reason or another—be it lymph-node involvement, extent of the lesion, age of patient, unsuitability on general grounds—only a few can be confidently submitted to surgery. But as in other sites, so in the pharynx, the excision must be wide. Minor surgery is unlikely to control cancer of the pharynx; conservative resections here, as elsewhere, seldom conserve the patient and often conserve the disease. If a diagnosis of cancer of the pharynx is established, if it is considered operable and suitable for operation, a laryngo-pharyngectomy is the operation of choice. The tissue removed extends from the base of the tongue, includes the epiglottis, the hyoid bone, the thyroid and cricoid cartilages, three rings of the trachea and the entire laryngopharynx. It leaves the patient with a permanent tracheotomy and a gap extensive and difficult to fill up. Many attempts at the closure of this gap and at the restoration of normal swallowing have been made. I will deal with the principles of repair only. Mr. Reidy will deal with the reconstructive surgery. There are, in fact, three methods available. (1) Partial closure with the original skin flap, leaving a pharyngostome. (2) Delayed closure by tube pedicles from the acromio-pectoral or cervico-pectoral areas; and (3) immediate reconstruction by means of a skin graft applied to a plastic tube. No. 3 is the ideal to aim at. Pharyngostomes and the inevitable leakage of saliva and difficulties with feeding should be avoided if possible. Delayed closure by tube pedicles often takes eight to twelve months, and demands many operations—sometimes half a dozen—and cancer patients do not tolerate this as well as the young and non-cancerous patients. The skin graft on plastic tube, when successful, permits normal swallowing within a few weeks. The incidence of stricture is, however, common and repeated dilatations, or even gastrostomy, become inevitable. The skin-grafted plastic tube is a great advance—yet it leaves much to be desired, and there is room for further attempts either by direct flap graft or by using frozen material such as the aorta or, preferably, the trachea.

Though most of my patients eventually died of their disease, there is yet enough encouragement in the occasional success and long survival to warrant the continuance of the effort.

Mr. Ronald W. Raven: The importance of cancer of the pharynx is evinced by the severe degree of suffering it causes the patient before it finally takes his life. For years cancer of the pharynx has presented us with a great challenge. We can never forget the endeavours of others in this difficult field—Wilfred Trotter, who did so much pioneer work, Lionel Colledge, and Harold Wookey.

The treatment of the various types of growth which occur in the nasopharynx still largely remains a radiotherapeutic problem. Radical surgery is valuable in carcinoma of the oropharynx; for example, I have one patient who had an advanced lesion in this situation which was considered unsuitable for radiotherapy, who is well and at work nearly four years after operation. In this paper I shall deal with the hypopharynx and recount some of my personal experiences with a series of 24 patients suffering from proved squamous-cell carcinoma treated by surgery. I use the term hypopharynx in its widest sense to include the part of the pharynx which extends from the glosso-epiglottic region to the pharyngo-œsophageal junction.

Clinical Condition of the Patients

The majority were suffering from extensive disease, and 50% had metastases in the regional lymph nodes. Some had been pronounced untreatable and were in great distress caused by stridor or dysphagia whilst awaiting their end; one had had a palliative gastrostomy and another a palliative tracheotomy. Others had received radiotherapy, but the disease was steadily advancing and there was nothing else to offer them but radical surgical treatment. It is against this bleak background that the results obtained by surgery should be judged. The sex and age incidence are shown in Table I.

Table I.—Sex and Age Incidence

Males	Females	Years						
11	13	37–39	40–45	46–50	51–55	56–60	61–65	66–70	71–75
Number of patients		2	0	2	1	6	7	5	1

Aspects of the Pathology

The requirements of the operation are based upon a knowledge of the behaviour and extent of the disease.

Origin.—As Trotter described it, the disease usually commences in the following areas: the epiglottis, glosso-epiglottic fold, aryepiglottic fold, pyriform fossa, posterior wall, and the post-cricoid region. The last situation is usually affected in females in this country, whilst males usually develop the disease in the higher parts of the hypopharynx. In some patients carcinoma is of multicentric origin. I cannot state the exact site of origin in many of my patients as the disease was so extensive; anterior penetration of the larynx was common, in others the thyroid gland was involved, and the growth extended from the cervical œsophagus to the junction of the oro- and hypo-pharynx.

Spread.—The growth has a high degree of malignancy; metastases occur in the regional lymph nodes early, and the disease spreads as shown in Table II.

Table II.—Spread of the Disease

Direct extension	Vertically in the wall to oropharynx and cervical œsophagus Anteriorly into larynx and trachea Laterally into thyroid gland and internal jugular vein Posteriorly into prevertebral muscles and cervical vertebræ
Lymphatic metastases ..	Deep cervical and recurrent laryngeal groups Prelaryngeal and pretracheal nodes may be affected
Hæmatogenous metastases ..	Lungs, liver

The lymphatics from the hypopharynx mainly drain through the supraglottic pedicle primarily into the deep cervical lymph nodes around the internal jugular vein extending from deep to the posterior belly of the digastric to the omohyoid. These nodes communicate with others in the neck including those under the anterior border of the trapezius. Initially metastases form in this group of nodes. When the larynx or cervical œsophagus is infiltrated metastases may also occur in the prelaryngeal, pretracheal and recurrent laryngeal groups of lymph nodes. A carcinoma localized in one half of the hypopharynx may affect the lymph nodes in the opposite side of the neck and bilateral nodes may be involved from the more extensive primary growths. The eradication of the diseased lymph nodes is a vital part of the surgical treatment.

Operability.—Certain facts can be elucidated to guide us, assuming that there are no general contra-indications present. A careful assessment of the general and local conditions is made. A history of many months usually means advanced disease, but sometimes this is found in patients with a short history. Signs of inoperability include fixity of the hypopharynx, diffuse lateral infiltration in the neck, and enlarged, fixed cervical lymph nodes. Pharyngoscopy shows the situation and upward extent of the growth and biopsy will reveal its nature; if the upper border reaches the base of the tongue operation may still be possible. Laryngoscopy shows marked œdema and any anterior extension into the larynx, but this does not exclude operation. Radiological examination with plain X-rays, a barium swallow and tomograms gives additional information regarding the local extent of the disease; if posterior infiltration through the pharyngeal wall into the prevertebral tissues is discovered operation is contra-indicated. In the lower group of neoplasms the extent to which the œsophagus is involved must be known to decide if it can be divided at a safe level below the growth. This is usually determined on exploring the neck, when the final assessment of the extent of the disease is made and a decision is reached about performing a radical operation. In my series of patients, one proved inoperable on exploration of the neck owing to invasion of the prevertebral tissues by the carcinoma; a palliative tracheotomy and gastrostomy were instituted to relieve the severe dyspnœa and dysphagia which were present.

Patients with dyspnœa should not undergo preliminary direct pharyngoscopy and laryngoscopy as spraying the pharynx and larynx with a solution of cocaine may cause a severe exacerbation requiring urgent tracheotomy which should be avoided if at all possible. In these patients I defer this examination until the patient is in the operating theatre for the major operation when a biopsy is

also done and a histological examination is made with the frozen section technique. In these patients I have also deferred the removal of septic teeth until after the major operation was performed. When there is respiratory difficulty I institute a tracheotomy under local anæsthesia as the initial step in the radical operation which is then continued under endotracheal anæsthesia. If severe dysphagia has caused dehydration and wasting a temporary gastrostomy is necessary to build up the general condition for three weeks before the major operation is done.

The Radical Two-stage Operation

Excisional Stage

Anæsthetic.—Intravenous Pentothal Sodium is usually given for the induction when severe dyspnœa is absent and an endotracheal tube with an inflatable cuff is gently passed into the trachea so that the growth is not injured. Endotracheal nitrous oxide and oxygen are then administered and the cuff of the tube is inflated with air; care is taken that it is not inserted so far in the trachea as to obstruct a bronchus. A large growth with marked œdema may prevent this, and the first steps are carried out under Pentothal or local anæsthesia and the trachea is divided as soon as possible for the administration of a general anæsthetic.

Monoblock dissection.—A quadrilateral flap of skin is raised from the neck based on the sterno-mastoid which is not being removed, and this part of the operation includes the removal of the hypo-pharynx, larynx, and the thyroid gland when it is infiltrated. Bilateral excision of the cervical lymph nodes is essential when they are found enlarged. The whole procedure constitutes a monoblock operation.

The regional lymph nodes.—These are examined and dealt with first. Affected lymph nodes may be found at operation which are not palpable clinically. When the primary growth is in the lateral wall of the hypopharynx, the lymph nodes may be involved only on that side of the neck, but the other side must be explored also. If the growth occupies both sides of the hypopharynx bilateral metastases are likely, and I have found the nodes are usually bigger and more numerous on one side, and this necessitates a complete block dissection. On the other side of the neck when the nodes are smaller and mobile they are removed completely but I leave this internal jugular vein and sternomastoid muscle.

The hypopharynx.—The upper and lower limits of the resection depend on the site and extent of the growth; the incisions should usually be 2·5 cm. away from its edge. Thus with the higher neoplasms the hyoid bone is removed and the lower section passes through the pharyngo-œsophageal junction. When the neoplasm is situated lower in the hypopharynx the hyoid bone remains and the cervical œsophagus is divided at the thoracic inlet. When it is doubtful if the incision has cleared the growth immediate histological examination with the frozen section technique of the divided pharynx and œsophagus is valuable. The trachea is usually divided between the second and third rings for the higher neoplasms, and between the third and fourth for the lower ones. When total thyroidectomy is necessary the parathyroids may be included; one of my patients developed mild tetany which was easily controlled by the usual treatment.

Reconstructional Stage

The quadrilateral skin flap is used for the new hypopharynx and is anastomosed to the divided oro- or hypo-pharynx above and the cervical œsophagus below; its lateral opening is closed later. The raw areas in the neck are covered with split-thickness skin grafts from the thigh. A polythene tube is inserted through the œsophageal opening into the stomach for feeding purposes. An interval of five to six weeks is usually allowed for healing and to enable the new skin tube to acquire a new blood supply from the prevertebral region before the final stage is carried out.

At the second operation the lateral cervical fistula is closed and the new skin hypopharynx is covered by full-thickness skin using rotation or hinged flaps from the neck or acromio-pectoral tubed pedicle grafts. A Ryle's tube is passed through the nose into the stomach for feeding purposes and a period of two to three weeks is usually allowed for healing before the patient is allowed to swallow.

I have carried out a laryngo-œsophago-pharyngectomy or laryngopharyngectomy in two stages for the majority of the patients in this series. They are radical operations and I have found the full-thickness skin tube with skin cover very satisfactory (Figs. 1 and 2; 3 and 4).

Post-operative Fistula

Sometimes an area of skin necrosis occurs after the operation with the formation of a fistula. This is usually in the suprahyoid region or posteriorly to the tracheostomy into the new pharynx. For instance the high variety occurred in 1 patient where the resection was made above the hyoid bone. I closed it by reflecting downwards a quadrilateral flap of the mucous membrane over the posterior aspect of the tongue and sutured its lower border to the freshened edge of the inner skin lining of the new hypopharynx. This was covered with full-thickness skin from an acromio-pectoral tubed pedicle graft. When the lower fistula is small it gradually contracts and closes spontaneously; larger ones may require a plastic operation to cure them or alternatively a Portex tube is inserted in the hypo-pharynx and into the œsophagus beyond the fistula and time is allowed for it to heal; in the meantime the patient can swallow.

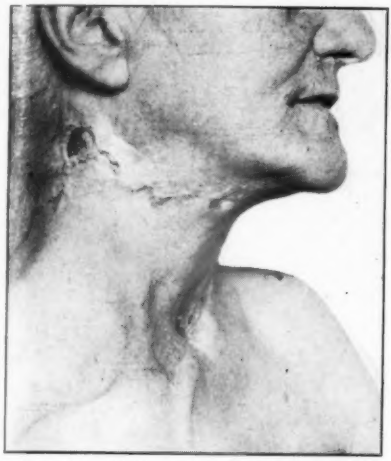

FIG. 1. — Patient aged 67 after laryngo-œsophago-pharyngectomy for an extensive carcinoma of the hypopharynx which had necessitated a gastrostomy. She is well forty-five months later and swallows everything.

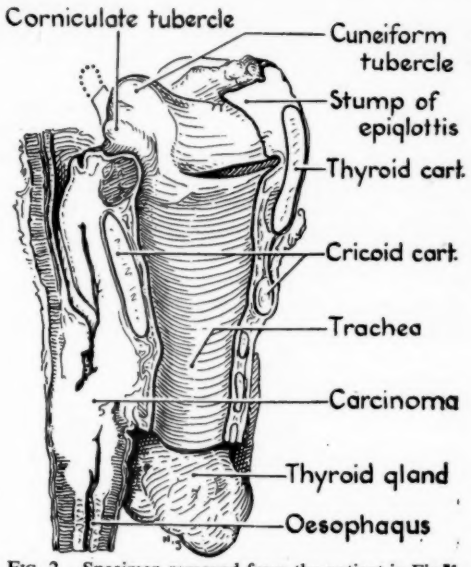

FIG. 2.—Specimen removed from the patient in Fig. 1. The carcinoma extends from the cervical œsophagus to the arytenoids.

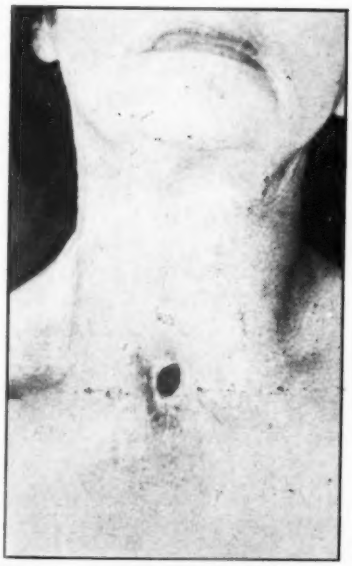

FIG. 3. — Patient aged 61 after laryngo-œsophago-pharyngectomy for a carcinoma of the hypopharynx. She is well twenty-three months later and swallows everything.

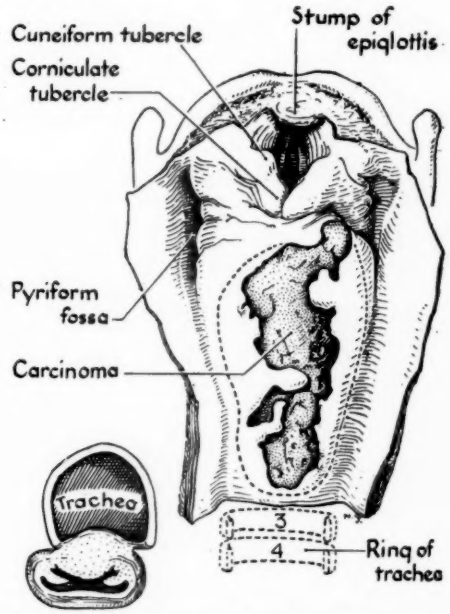

FIG. 4.—Specimen removed from the patient in Fig. 3. The carcinoma extends from the cervical œsophagus to just below the arytenoids, the marked œdema of the latter is evident. The inset shows the growth invading the œsophago-tracheal septum and bulging into the trachea.

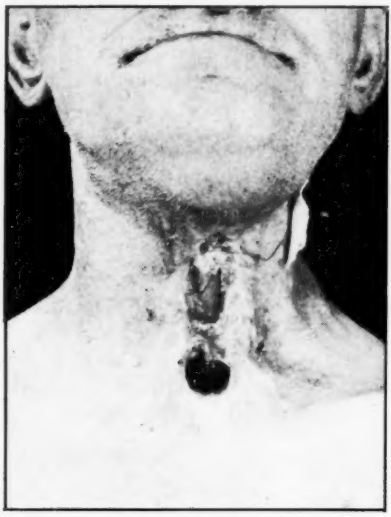

FIG. 5.—Patient aged 64 who had an extensive carcinoma of the hypopharynx with a metastasis in a cervical lymph node treated with high voltage X-radiation. The disease was extending and a laryngopharyngectomy was performed with the formation of a median pharyngeal fistula. A Portex tube has been inserted and the irradiation changes in the skin are shown.

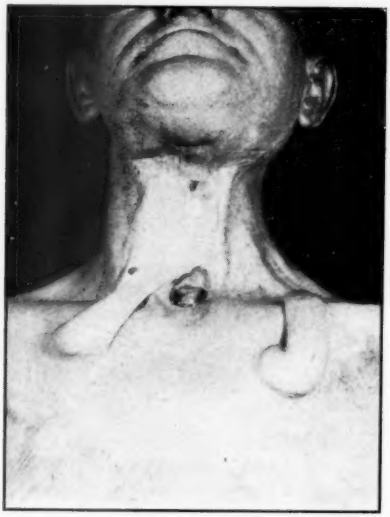

FIG. 6.—Same patient as in Fig. 5 showing acromio-pectoral tubed pedicle skin grafts brought up to the neck in stages; the left one is kept in reserve. The fistula has been closed by an inner hinged full-thickness skin graft from the neck and covered by the right acromio-pectoral graft.

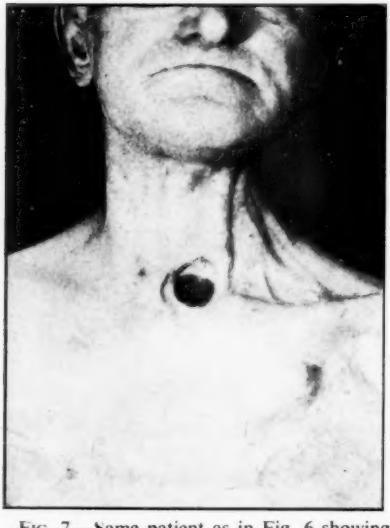

FIG. 7.—Same patient as in Fig. 6 showing the final result. The patient is well twenty-six months later and swallows everything.

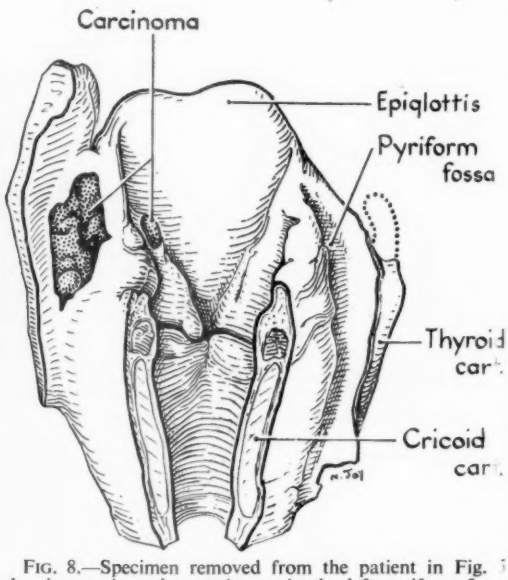

FIG. 8.—Specimen removed from the patient in Fig. 5 showing an irregular carcinoma in the left pyriform fossa 3·8 × 1·3 cm. which reaches the left aryepiglottic fold medially and a nodule of growth projects on the posterior surface of the epiglottis at the level of the centre of the ulcer. At the posterior margin of this nodule is a small perforation communicating with the ulcer in the pyriform fossa.

One-stage Operations with Primary Closure of the Pharynx

These procedures are sometimes possible but are less radical and should only be done for an early growth especially in the lateral wall of the pharynx. For instance, in one patient I excised the hypopharynx and larynx and performed an end-to-end anastomosis between the upper segment of the divided hypopharynx and the pharyngo-œsophageal junction and he swallowed perfectly five weeks later. This operation was possible because the patient had a severe fixed cervical kyphosis and the divided ends could be brought into apposition without tension. For another patient with an early carcinoma in the left pyriform fossa I performed a partial pharyngectomy with conservation of the larynx and reconstructed the pharynx. Bilateral excision of the cervical lymph nodes is always necessary when they are enlarged.

Staged Radical Operations After Unsuccessful Radiotherapy

When a radical operation is necessary after radiotherapy, for an uncontrolled or recurrent carcinoma, a number of difficult technical problems are present due to degenerative changes in the skin of the neck. I have used two techniques when dealing with these patients with satisfactory results.

(1) *Conservation of a strip of the posterior pharyngeal wall.*—This is possible when the carcinoma is situated away from the posterior wall and then its lateral borders are sutured to the skin of the neck thereby creating a median pharyngeal fistula. A Portex tube is inserted in the hypopharynx and beyond the fistula into the œsophagus so that the patient can swallow. An interval is allowed for the skin of the neck to improve sufficiently so that a plastic operation can be done to close it; several months may be required and during this time bilateral acromio-pectoral tubed pedicle grafts are prepared. To close the fistula it is sometimes possible to reflect a quadrilateral skin flap, hinged on one edge of the fistula, turn it over and suture it to the opposite edge to provide an inner skin lining. This is covered by the full-thickness skin of one acromio-pectoral graft (Figs. 5, 6, 7 and 8). Alternatively, both acromio-pectoral grafts are used for the inner skin lining and outer skin cover.

(2) *Use of a narrow quadrilateral skin flap.*—When the position and extent of the carcinoma necessitate removal of the whole hypopharynx the quadrilateral skin flap is cut sufficiently narrow so that it will probably retain its blood supply and survive. At the same time it must be wide enough to cover the prevertebral tissues and form a posterior wall for the skin pharynx. Its upper border is sutured to the posterior wall of the divided hypopharynx, the lower border to the posterior wall of the divided œsophagus and the free edge to the skin of the opposite side of the neck. The anterior wall of the divided hypopharynx is sutured to the skin of the submaxillary region and the patient is left temporarily with a posterior skin gutter. Acromio-pectoral tubed pedicle grafts are then prepared for the construction in stages of the anterior wall of the skin pharynx and to provide it with full-thickness skin cover.

When the vitality of the skin of the neck is greatly impaired, acromio-pectoral tubed pedicle grafts must be prepared beforehand and be ready for use when the excision of the hypopharynx is performed so that a posterior wall for the skin pharynx can be provided and the prevertebral tissues covered.

End-results with Surgical Treatment

The periods of survival after these operations in 23 patients are set out in Table III. One additional patient was found to be inoperable on exploration of the neck and a palliative tracheotomy and gastrostomy were instituted. There was no operation mortality.

Table III.—End-results with All Types of Operation

	Period in months after operation									
10 patients alive..	3	5	6	7	9	23	23	26	26	45
10 patients died of cancer ..	4	4	8	12	12	12	20	23	23	33
3 patients died of other cause ..	2	11	30							

The results of surgery should not be judged only by survival periods, each patient is an individual problem to solve with serious symptoms requiring immediate relief. In many patients the disease in the hypopharynx is extensive with infiltration of the larynx and possibly the thyroid gland, and metastases in the regional lymph nodes are often present rendering the condition unsuitable for irradiation treatment. In addition a number have severe dyspnœa or stridor requiring a tracheotomy. No treatment other than surgery was possible for the majority of my patients; they were relieved completely of their distressing symptoms and given the possibility of more permanent benefit. After operation the patients are happy, grateful, live useful lives, dress normally, and some return to work. They swallow everything easily and no patient in my series has developed a fibrous stricture at the junction of skin pharynx with the œsophagus or elsewhere. Their ability to speak is variable but this is not so good as after laryngectomy. The longest survival period at present is forty-five months; this patient was aged 67 with an extensive carcinoma causing severe dysphagia for which a palliative gastrostomy was performed elsewhere and she remains well and swallows everything perfectly—the gastrostomy was allowed to close. As a result of my experience I can recommend these operations knowing they have considerable palliative value and it is hoped that time will prove that some patients may be permanently cured.

ACKNOWLEDGMENTS

I thank Dr. L. A. Morris and Dr. A. Chester for helpful co-operation in the anæsthesia of the patients my registrars, house-surgeons and the nursing staff for their help; and Portland Plastics, Ltd., who supplied me with Portex tubes.

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Mr. J. P. Reidy: In this discussion I am concerned only with the process of repair, and by this I mean the reconstruction of the cervical œsophagus to allow of normal swallowing and the passage of food from mouth to stomach.

The reconstruction of an œsophagus involves at least two layers of tissue—a lining and a cover. At present, skin is used to provide lining and cover, and, of the two, the more difficult task is the provision of a lining which will not contract or produce a stricture.

In brief: (1) The lining may be made of flap skin which has its own blood supply and does not contract, and once completed with proper cover such an œsophagus gives no trouble. The reconstruction, however, requires several stages in the preparation and transfer of the skin flaps.

(2) The lining may be made of a sheet of Thiersch graft inserted on a tube and covered with flap skin. This allows of primary excision and reconstruction in one operation. The use of a Thiersch graft carries with it the risk of contraction along its whole length, or constriction at its junction with the upper end of thoracic œsophagus.

In these cases of pharyngolaryngectomy, the provision of a cervical œsophagus is an essential, otherwise the patient is left with a large pharyngostomy above, and two openings in the lower neck, the œsophagus and the tracheostomy. Saliva dribbles from above and causes excoriation of the neck skin. Furthermore, saliva flowing into the trachea at best afflicts the patient with continuous attacks of explosive coughing, and at worst with bronchopneumonia and death. The use of dressings on the neck to mop up the salivary flow is not only difficult but ineffective. Having regard to this uncomfortable post-operative state, to the age of the patient and to the prognosis, the surgeon must make the choice between, on the one hand, a rapid reconstruction in one stage by a Thiersch graft on a tube with its possible shortcomings, and on the other, a reconstruction with flap skin for lining, requiring more than one operation, but producing a relatively trouble-free result.

The operation of pharyngolaryngectomy is a formidable procedure, but there appears to be no satisfactory alternative to this mutilating surgery. A low operative mortality is essential together with rapid steps in reconstruction to make the whole procedure worth while.

In 1913, Wilfred Trotter described pharyngotomies with excisions, and with reconstruction using local skin flaps. His endeavour was always to preserve the larynx and pharynx (Fig. 1A).

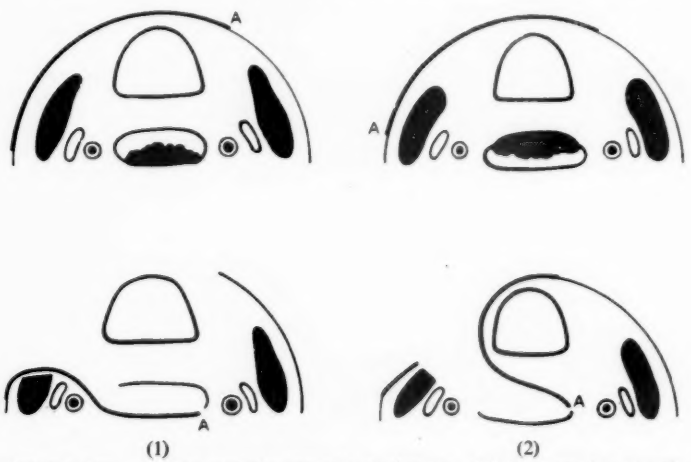


FIG. 1A.—Trotter's flap. (1) For posterior growth of pharynx. (2) For anterior growth of pharynx.

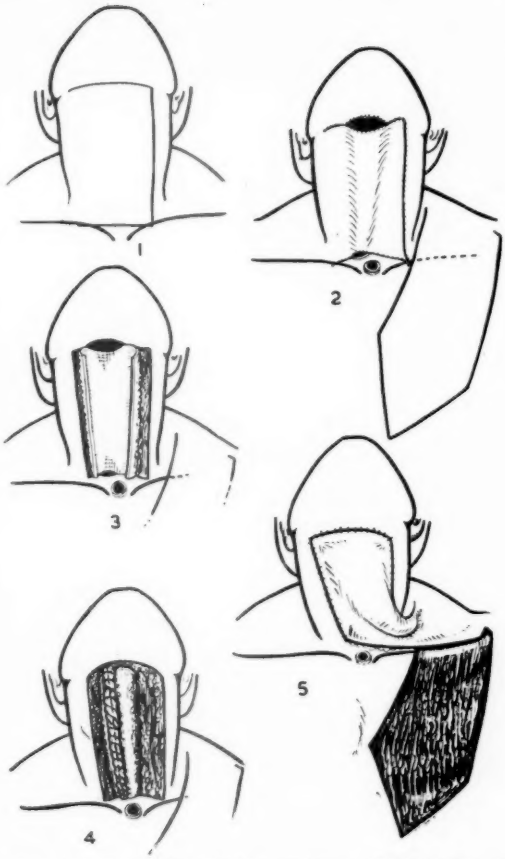


FIG. 1B.—Total pharyngolaryngectomy. (1) Broad transverse flap on neck, outlined. (2) After primary excision. Neck flap replaced. Three stomata. (3 and 4) Transverse neck flap inturned and sutured to enclose pharyngostome and œsophagus, providing flap lining. (5) Acromiothoracic flap applied for cover.

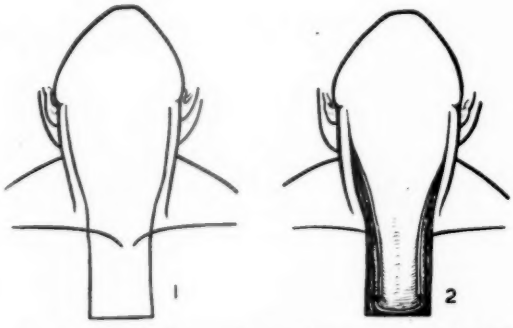


FIG. 1C.—Total pharyngolaryngectomy. Long U-flap for (1) exposure and (2) reconstruction. (Mr. E. E. Lewis, Cardiff.)

THE CONSTRUCTION OF FLAPS (FIG. 1B, 1C)

(1) Where the neck skin has been irradiated, the blood supply will be diminished. Any form of flap, particularly long and transverse, will be liable to slough. If this occurs there will be breakdown of lining whether of flap or of Thiersch graft.

(2) Reconstruction of the œsophagus with *flaps for lining* is likely to give a more certain and trouble-free result. The drawback is that more than one operation is required with an interval of weeks between.

(3) Ideally, flap skin for lining is desirable, preferably inserted at the primary excision. It is, however, *not justifiable* to delay primary excision in order to prepare appropriate skin flaps.

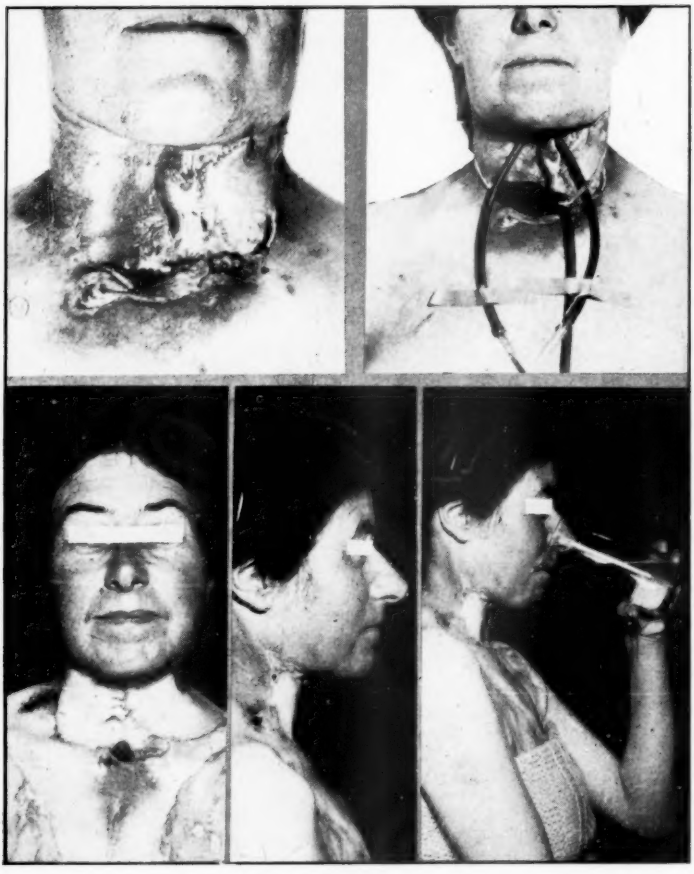
It may be possible to devise a skin flap for immediate use as lining, at primary excision, without the need for previous preparation, and so complete the operation in one stage.

(4) When the primary excision is performed, and the trachea and œsophageal stumps are sutured to skin on the lower part of the neck, care must be taken to place a skin bridge between the two. Close approximation of œsophagus and trachea makes suturing of lining flap very difficult (Fig. 1D).

FREE GRAFTS

In 1950, V. E. Negus advocated pharyngolaryngectomy for hypopharyngeal carcinoma and immediate repair using a Thiersch graft wrapped around a polythene tube. This tube and graft were inserted into oropharynx above and œsophagus below to reform the cervical œsophagus, and the skin flaps of the neck were applied as cover. Negus left in his tube for six months, but has reported some difficulties arising out of this.

In 1951, Mr. Negus gave me the benefit of his advice and I followed certain lines, after a close study of the literature and the methods employed by previous surgeons. My incisions were Z-shaped to allow wide exposure from broad-based flaps (2A). These flaps could be adjusted on each other in closing up, so as to gain length vertically—particularly useful when œsophagus and trachea are divided at level of 6 or 7 ring of trachea. The lateral flaps and single transverse flap do not allow of much adjustment vertically. The polythene tube was modified in shape finally to produce a long 10-in. funnel,



1 2 3 4 5

FIG. 1D.—Total pharyngolaryngectomy (Sir Stanford Cade) for carcinoma of the larynx. Reconstruction œsophagus. T P flaps. (1) After total pharyngolaryngectomy. Transverse neck flap (previously irradiated) has partly sloughed. (2) Before repair. Tracheostomy tube in place. Stomach tube in œsophagus. Tubes in pharyngostome to suck away saliva. (3, 4 and 5) After flap repair of cervical œsophagus.

2½ in. oval at upper end, tapering to 1 in. diameter at half-way, and narrowing further to ½ in. diameter distally. This long end acted as a whip well within the œsophagus, and produced no "sharp edge" necrosis of œsophagus as with the earlier type tube. The smallest diameter allowed passage of a Ryle's tube, but it has not been necessary to use the whole length of 10 in. The posterior aspect of œsophagus is divided vertically to make a large lumen, and the tube and graft are inserted within the œsophagus below and within the oropharynx above to lie behind the tongue (Fig. 2A, B, C, D).

The graft is stitched with plain catgut to the margin of œsophagus and to mucous membrane of oropharynx. Three wire or stout nylon sutures are run transversely through neck going through skin, sternomastoid muscles and through polythene tube with its graft. The sutures are tied or fixed on the skin surface and prevent the polythene tube from sliding down.

In one case of mine the tube slipped and produced necrosis of graft at level of manubrium.

A pressure dressing is applied to the neck in order to compress the skin flaps on to the underlying graft. A good thick neck dressing also immobilizes the head and neck. The dressing is maintained for three weeks, though changed every week.

In my short series of cases, the polythene tube has been removed through the mouth during the third week, in order to avoid risk of pressure necrosis by tube on graft.

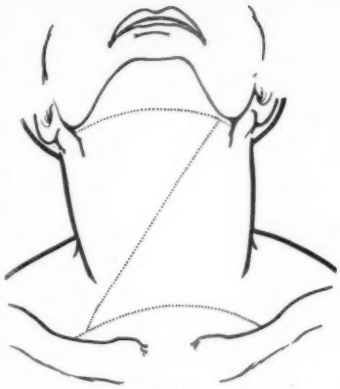


FIG. 2A.

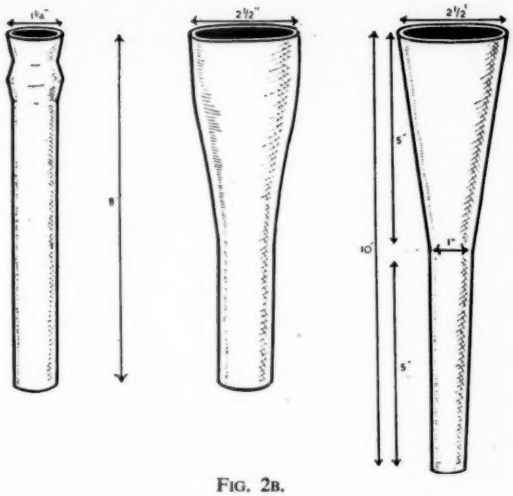


FIG. 2B.

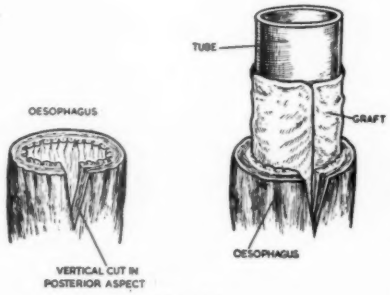


FIG. 2C.

FIG. 2.—Reconstruction of cervical œsophagus by Thiersch graft on a Portex tube. A, Z-incision for exposure. B, Types of polythene tubes. C, Insertion of tube and graft into œsophageal stump. D, Total pharyngolaryngectomy (Sir Stanford Cade) for carcinoma of pyriform fossa. Post-operative appearance.

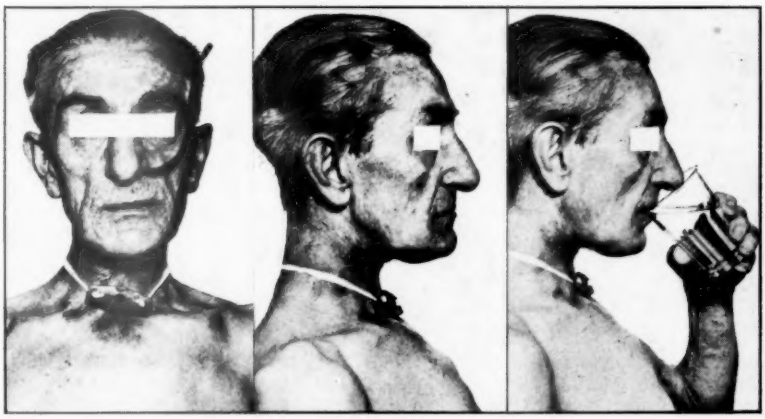


FIG. 2D.

The patient is fed through a Ryle's tube or ordinary stomach tube running through one nostril, nd inside the polythene tube to the stomach. A high protein fluid diet is given through the tube see Table I). When the polythene tube is removed, fluid and soft solids are given by mouth normally, radually increasing to ordinary solids. The patients normally gain weight, and may gain up to 2 st.

TABLE I.—HIGH PROTEIN, HIGH CALORIE FLUID DIET IN PHARYNGOLARYNGECTOMY

Stage I		Stage II	
Milk	3 pints	Patient taking food by mouth. Diet altered	
Casilan	6 oz.	Milk	2½ pints
Sucrose	2½ oz.	Casilan	5½ oz.
Glucose	4 oz.	Glucose	2½ oz.
*Liq. calcii hydrox. sacch.	25 oz.	Vitamins	Continued
2,700 calories			

Radiostoleum
Calciferol
Becosym
Nicotinamide
Ascorbic acid
Ephynal
Pancreatin
Thyroid extract
Neo-ferrum
Sodium citrate

*Calc. hydrox. discontinued after one week.

THIERSCH GRAFT LINING

(1) Reflection of neck skin is preferable in two flaps on broad bases rather than in one transverse flap. Z flaps allow of some rearrangement to pay the transverse excess into the vertical.

(2) Previous irradiation enhances risk of sloughing of the flaps. It also appears to increase the risk of fibrosis and contraction of the skin graft.

(3) The graft should be cut in one piece about 8 in. by 4 in., of medium thickness and from hairless skin, e.g. the inner aspect of a thigh. The graft is applied, raw surface outwards, to the polythene tube, and stuck on with Mastisol.

(4) Firm pressure dressing around the neck is essential for success—for at least fourteen days—and neck movements must be prevented.

(5) The polythene tube is removed during the 3rd week, and normal feeding by mouth commenced. Keeping the polythene tube longer carries with it the risk of ulceration by the tube through the graft, and through the covering neck skin. Constriction may occur only at the junction of graft with normal œsophagus, but this may give no symptoms, although it may be apparent radiologically.

(6) Contraction of the whole "grafted œsophagus" may occur rapidly within six weeks of operation or more slowly. In either case, it is unlikely that passage of bougies at intervals will do more than provide temporary relief. In the long run, it is quicker to excise the whole grafted œsophagus and to reconstruct with flaps. Meanwhile, a gastrostomy is essential.

(7) The tracheostomy tube is discarded as soon as possible.

(8) Where a tracheotomy has been performed some time prior to primary excision, the method of Thiersch graft on a tube should not be undertaken. There is grave risk of infection breakdown, bronchopneumonia and death.

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Mr. Gavin Livingstone: In cancer of the upper pharynx irradiation of the primary lesion is probably the best treatment, but in the mid-pharynx and hypopharynx results of irradiation are so disappointing that I think surgery is at present the method of choice. There has been a change of outlook on pharyngeal surgery in the last few years because of the straightforward convalescence of the patient following laryngectomy compared with the pre-penicillin era, and I feel the fate of the larynx should not interfere with the planning of the operation.

In all cases of post-cricoid carcinoma and in most pyriform fossa lesions the larynx will have to be removed. In these cases if glands are present a block dissection should take place at the same time as a pharyngolaryngectomy where the complete segment of the pharynx should always be removed. Another indication for removing the larynx is where the recurrent laryngeal nerves are involved or may be injured, leaving the patient with a bilateral abductor paralysis which will necessitate a permanent tracheotomy and possibly a laryngectomy later.

Mr. R. Raven has been advocating a two-stage reconstruction in these pharyngolaryngectomies. On this question I feel that the better approach is to plan the operation so that there is a primary reconstruction, complete if possible, but at any rate of the food channel, as the patient is then saved that rather unpleasant three weeks following the primary operation until the secondary closure is carried out. At present I think the Thiersch graft on a polythene tube seems to be the best method. Two advantages of this are that any length of the pharynx removed can be bridged, and that the method can be used after the neck has been irradiated where any reconstruction using local skin flaps will probably break down owing to the sloughing of the flaps. I do not think it justifiable to delay the primary operation for six to eight weeks while pedicle skin grafts are prepared.

In point of fact the Thiersch graft reconstruction is falling into disfavour due to the number of cases which develop strictures. I think the reason for this is that there has been no standardization of the method. For example, the tubes used may vary in size, length or shape with the individual surgeon, and again, there is great variation in the time tubes are allowed to remain in situ. In my experience, strictures do not always develop, and, when they do, they are usually at the lower end at the œsophageal graft junction. I always remove the hyoid bone with the larynx, and because of this a stricture is unusual at the upper end. Great attention must be paid to detail. It is small details and variations in technique which decide the success or failure of this method of reconstruction.

In one case where a stricture did develop two months after operation, I inserted a small polythene tube about an inch in length, the size of a No. 10 intratracheal catheter, and had the upper end flanged so that it would not slip through the stricture. The patient is wearing this tube permanently, and although I have removed it for inspection on two or three occasions, there has been no suggestion of ulceration or discomfort, and as the reconstructed pharynx is entirely insensitive, the patient is able to adjust the tube should it become dislodged or temporarily blocked.

An œsophageal-tracheal fistula may occur from too long or too big a polythene tube, or one which is not removed soon enough. I remove mine in fourteen days.

A patient in whom one of these fistulas occurred vomited while he was being fed through a feeding tube, and the stomach contents regurgitated up the œsophagus and went into the trachea. In spite of aspiration infection occurred and the patient died six weeks later from a lung abscess, though the fistula had nearly healed. In future I would use a cuffed feeding tube so that the cuff can be inflated around the tube in the œsophagus to prevent any regurgitation of food. This would be a safeguard against the recurrence of such a tragedy.

Conclusion.—If this mutilating operation is to hold a permanent place in the treatment of pharyngeal cancer, a one-stage operation can add greatly to the patient's comfort during convalescence, and can shorten his stay in hospital. At present until the plastic surgeons, who should be intimately associated with this operation, can devise a one-stage reconstruction I think that the Thiersch graft is the method of choice. But a technique must be perfected which will minimize the chances of strictures.

Mr. V. E. Negus said that the discussion had centred on growths arising at or near the mouth of the œsophagus in the post-cricoid region. He proposed, therefore, to speak mainly of this type.

There were many cases of growths on the outside of the larynx which could be dealt with effectively by Trotter's method of transthyroid lateral pharyngotomy.

With regard to post-cricoid growths it was very much better to make the decision that if anything were to be done it must be by radical surgery. He was averse to loss of time and added discomfort to the patient by attempts to treat these growths with irradiation which, in his experience, had no prospects of cure. The operation resolved itself into removal of the larynx with part of the pharynx and upper end of the œsophagus, followed by immediate primary repair by means of a plastic tube covered by a skin graft. At the operation it was necessary to carry out block dissection; the fascia, glands, sternomastoid and internal jugular vein being left attached to the pharynx and larynx. The hyoid bone and usually four rings of the trachea were taken away, and also half of the thyroid, a portion being left, if possible, in order to avoid subsequent deficiency of thyroid and parathyroid hormones.

Professor R. S. Pilcher said that Trotter's insistence on preserving the larynx might be untenable to-day, but equally untenable was the rejection of his conservative operation of lateral pharyngotomy. Brevity of treatment was an important part of palliation, which should be assessed by the duration of relief and not by survival alone. Where the outlook was bad because of glandular metastases conservative treatment of the pharynx with the prospect of early recovery of function might be the most useful form of surgery.

Long-term results.—Out of 100 consecutive and unselected cases admitted to University College Hospital in 1927 to 1936, 7 survived five years or more without pharyngeal recurrence after conservative operations on the pharynx. He was not aware that this rate of salvage from all comers had been bettered.

[*April* 17 and 18, 1953]

MEETING AT THE QUEEN ELIZABETH HOSPITAL, BIRMINGHAM

Programme

[*April* 17, 1953]

Operations and Demonstrations

Demonstrations:

Specimens to Demonstrate the Nature of Ulcerative Colitis.—Mr. B. N. BROOKE.

Pathological Demonstrations.—Dr. J. G. JACKSON.

Cases Demonstrating the Use of the Epithelial Inlay Technique in Excision and Repair, with Special Reference to Tumours of the Jaws.—Mr. O. T. MANSFIELD and Mr. R. O. WALKER.

Demonstration of X-rays.—Dr. O. SMITH.

Operations:

(1) Thyroidectomy. (2) Retro-pubic Prostatectomy.—Mr. R. K. DEBENHAM.

Ulcerative Colitis—Excision of Rectum and Revision of Ileostomy for Prolapse.—Mr. B. N. BROOKE.

Partial Gastrectomy.—Mr. R. P. SCOTT MASON.

Mitral Valvotomy.—Mr. A. L. D'ABREU.

The following Papers were read:

A Method of Using Intravenous Procaine in the Treatment of Fractured Ribs.—Mr. GILROY BEVAN.

The Nature of Ulcerative Colitis: Its Definition and Cause.—Mr. B. N. BROOKE.

Blood and Fluid Loss at Operation.—Mr. A. J. H. RAINS.

Lawson Tait.—Emeritus Professor SEYMOUR BARLING.

The Present Management of Paralytic Ileus.—Mr. J. A. C. EDWARDS.

The Anatomy and Nerve Supply of the Crura of the Diaphragm with Special Reference to the Repair of Hiatus Hernia.—Mr. J. LEIGH COLLIS.

Acidosis after Uretero-colic Anastomosis: a Study of Its Control.—Mr. N. C. ROGERS (introduced by Mr. H. DONOVAN).

Relief of Pain of Pancreatic Origin.—Mr. D. M. MORRISSEY.

Duodenal Obstruction in the Newborn.—Mr. A. GOUREVITCH.

[*April* 18, 1953]

Operations:

(1) Partial Cystectomy. (2) Millin Prostatectomy. (3) Nephrectomy. (4) Orchidectomy. (5) Demonstration: Ascending Pyelograms.—Mr. H. DONOVAN.

Partial Thyroidectomy.—Mr. A. GOUREVITCH.

Œsophagectomy. (Fluid Loss Studies Were Made During This Operation).—Mr. A. L. D'ABREU.

(1) Heller's Operation. (2) Left Pneumonectomy. (3) Second-stage Right Thoracoplasty. (4) Bronchoscopy.—Mr. J. LEIGH COLLIS.

Section of Comparative Medicine

President—C. L. OAKLEY, B.Sc., M.D., B.S., M.R.C.S., L.R.C.P.

[*March* 18, 1953]

DISCUSSION ON SOME BIOLOGICAL ASPECTS OF MUCIN

Professor W. T. J. Morgan (Lister Institute of Preventive Medicine): *Some Aspects of the Chemistry of Mucins.*

Introduction

The term "mucin" is best used in a physiological sense, that is to denote a viscous secretion, the chemical nature of which may be quite unknown. To gain an insight into the chemistry of mucins involves a study of the chemical nature of the various components which, as might be expected, vary from one mucin material to another. In many instances the chemical entities isolated from a mucous secretion do not possess the characteristic mucilaginous behaviour of the native mucin, and indeed little is known concerning the nature of the forces of interaction and association between the component residues in mucins which bring about the formation of the enormous, highly viscous, polymolecular aggregates met with in the native physiological secretions. Only carbohydrate complexes which contain amino-sugar are considered in this discussion. The mucilaginous, nitrogen-free plant and bacterial gums will not be referred to.

Numerous studies involving the isolation and characterization of the molecular entities in mucins have been carried out since Eichwald in 1865 stated that mucins were composed of albumin and a sugar radical. Subsequently the extensive researches of Hammersten and of Müller in the 1890s showed the importance of this ill-defined group of substances and recognized some of their more characteristic properties such as their ready decomposition by alkali, their high content of carbohydrate and the fact that in many instances they are not coagulated by heat. However, an examination of the methods used at this time to isolate the materials makes it appear probable that the preparations obtained were mixtures and that besides the major mucilaginous component there were present other carbohydrates and protein moieties. It must be emphasized, however, that even to-day, with all the modern techniques of physical chemistry, it is exceedingly difficult to establish satisfactorily the homogeneity of these materials, the physical properties of which are so anomalous.

Classification

Meyer (1938) attempted to define and classify the large group of substances which are referred to in the literature under the heading of mucopolysaccharides, mucoids, glycoproteins, mucoproteins and mucins. Stacey (1946) extended and to some extent modified Meyer's scheme. In considering materials in this complex field it is certainly a great help if one can characterize the main groups and develop some rudimentary classification. Classification, however, must remain highly unsatisfactory and arbitrary as long as the various complex materials under consideration are ill-defined and all too frequently seriously contaminated with other substances.

The simplest materials under discussion are the mucopolysaccharides. A mucopolysaccharide contains amino-sugar but not amino-acids. There are neutral mucopolysaccharides such as the specific polysaccharides of *Shigella shigæ* and the pneumococcus Types IV and XIV, and there are acidic mucopolysaccharides which contain glycuronic acid alone, as in hyaluronic acid, or with the further addition of sulphuric acid groups as in chondroitin-sulphuric acid and heparin.

The materials next in order of complexity consist of neutral and possibly acid mucopolysaccharides firmly bound to an amino-acid-containing residue. Meyer considers mucoids as those complexes which contain more than 4% hexosamine but he nevertheless appreciates that on the basis of hexosamine content alone it is not possible to differentiate sharply this group of substances from other materials found in mucin.

It seems useful to call the type of complex which contains 70% or so of carbohydrate as the major component, a mucoid, and important examples of mucoids are to be found in those substances which, by virtue of their specific serological properties and their occurrence on the erythrocyte surface and in the tissue fluids and secretions, are responsible for the human blood-group characters.

Materials which contain considerably less carbohydrate bound to protein can be termed, as they frequently are, mucoproteins, as this designation indicates clearly the nature of the major component.

Examples of substances falling within this group are the carbohydrate-containing proteins of serum and egg white, the gonadotrophic hormones and the material recently isolated from urine which inhibits the hæmagglutination brought about by certain viruses. It must be recognized, however, that there is probably no sharp distinction between the mucoids and mucoproteins. The polysaccharide content of materials of this kind which have different origin and function almost certainly varies continuously from a high value to a low one, equivalent to not more than a few per cent of the total complex.

There remain the glycoproteins, those proteins which contain about 1 or 2% only of firmly bound carbohydrate. To this class belong crystalline egg albumen and certain preparations of serum albumin. Meyer has pointed out that those proteins which crystallize best, for example, pepsin, chymotrypsin and trypsin, possess no carbohydrate component.

Finally, I will describe in greater detail the chemical nature of two materials which are of outstanding biological importance, and which have recently been studied in considerable detail. They may be considered as typical examples of the class of mucoids and mucoproteins respectively.

Blood-group Mucoids

The classical blood-group characters shown by human erythrocytes and secretions are now known to be due to the presence of mucoid substances. These materials contain a major polysaccharide component, which constitutes not less than two-thirds of the total substance, firmly joined to an amino-acid-containing moiety. The mucoids which possess the A, B, H and Lewis (Le^a) serological characters have each been isolated in a substantially homogeneous condition and appear to be qualitatively identical. Each serologically specific mucoid contains the sugars L-fucose, D-galactose and the two amino-sugars D-glucosamine and D-chondrosamine (galactosamine) and eleven amino acids. They behave similarly when treated with weak acid or alkali at 100° C. and are readily decomposed with complete loss of their specific serological characters when treated with certain purified enzyme preparations obtained from *Cl. welchii* and *T. fœtus*. Each substance rapidly loses L-fucose on treatment with *N*-acetic acid at 100° C. and the material, indiffusible through a cellophane membrane, which remains is found to have developed the property of precipitating with pneumococcus Type XIV horse anti-serum. Some analytical figures for the serologically specific materials are summarized in Tables I and II from which it may be concluded that the group mucoids all belong to a

TABLE I.—PHYSICAL CONSTANTS

Property	Blood-group substance A	B	H	Le^a
Partial Specific Volume	0·635	0·600	0·636	0·643
Diffusion constant $D_{20} \times 10^7$ (1·0%)	1·6*	0·51†	1·21	1·37
Sedimentation constant $S_{20} \times 10^{13}$ (0·5%)	6·7	12·0	6·6	6·7
f/f_0	3·2	5·6	4·2	3·8
Axial ratio	60	200	100	about 90
Particle weight	$2·6 \times 10^5$	$1·8 \times 10^6$	$3·2 \times 10^5$	$2·7 \times 10^5$

*0·81% †0·2%

TABLE II.—ANALYTICAL FIGURES (AVERAGE VALUES) FOR PREPARATIONS OF THE HUMAN BLOOD-GROUP SUBSTANCES

	Rotation	Nitrogen %	Acetyl %	Hexosamine %	Reduction %	Fucose %
A-substance	+15°	5·7	9·0	37	56	18
H-substance	−30°	5·3	8·6	31	54	13
Le^a-substance	−40°	5·0	9·9	32	57	12
B-substance	0°	5·7	7·0	20	50	18

special type of polymolecular aggregate that contains a common or basic molecular framework which, by virtue of certain quantitative variations in the constituent molecules, develops a different stereochemical configuration which is the structure ultimately responsible for the characteristic immunological specificity. It has not yet been possible to separate the polysaccharide and amino-acid-containing residues and retain the original blood-group specificity. In all persons one or more of these materials are major components of gastric and intestinal mucin and saliva and are also found in large quantities in meconium, the first stool of the newborn.

Mucoprotein Virus Inhibitors

The observation that influenza viruses bring about the agglutination of chicken erythrocytes was followed by the discovery that a powerful virus inhibitor was present in normal urine and egg-white. The former material has recently been isolated by Tamm and Horsfall (1952) in a form which is apparently free from other contaminating substances. The material, which contains amino acids and sugars, is exceedingly active in inhibiting the agglutination of erythrocytes by influenza, mumps and

Newcastle disease viruses, has a particle weight of the order 7×10^6 and consists of thread-like molecules which have an axial ratio of about 100. The material is a typical mucoprotein, contains 12·6% N, 5·2% S and gives 33% reducing substances, and 9·2% hexosamine after acid hydrolysis. Gotteschalk (1952) states that the material contains 5·4% galactose, 2·7% mannose, 1·1% fucose and 7·6% of amino-sugar which is a mixture of glucosamine and chondrosamine. Similar results have been obtained by Odin (1952). Gotteschalk has studied the changes which arise when the mucoprotein is acted on by influenza virus or, more correctly, by the enzymic equipment of the virus particle. He found that about 1% of the total mucoprotein is split off and can be separated from the remaining material by simple diffusion through a cellophane membrane. The dialysable split product was identified as a carbohydrate-peptide compound or more exactly as N-substituted fructosamine. After the action of the virus the mucoprotein, although changed, remains homogeneous and its electrophoretic mobility, originally about -9×10^5 cm.^{2} sec.$^{-1}$ volt.$^{-1}$, is decreased by about 20%. The changed mucoprotein is no longer able to inhibit the action of the virus on erythrocytes.

From the results of his experiments Gotteschalk concludes that the mucoprotein is a conjugated protein containing as prosthetic group a polysaccharide of relatively small size, maximum value 10,000, and suggests that about 200 such groups may be linked to each protein molecule on the basis of a particle weight of about 7×10^6.

A detailed study of virus inhibitors of this kind may well reveal the way "mucin", when present as a mucous film in the respiratory tract, is able to modify the course of virus infection.

In conclusion one might say that we are getting to know something of the composition, structure and mode of linkage of the component molecules of native mucins and that a knowledge of these properties will most probably allow us to understand more clearly at least some of their biological properties.

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Dr. A. E. Pierce (Lister Institute of Preventive Medicine): *Specific Antibodies at Mucous Surfaces.*

The detection of antibodies at mucous surfaces has been concerned with those in the mucin derived from intestinal mucosa and recovered from the fæces—the so-called "copro-antibody"—and those occurring in the mucin of the vagina, uterus and the bronchi.

The copro-antibodies and antibodies occurring in the bronchi have been the subject of medical research, while antibodies detected in mucin from the uterus and vagina have been exclusively observed in the bovine and are of considerable veterinary interest.

Copro-antibodies were first reported by Davis in 1922. He demonstrated agglutinating antibodies to Shiga and Flexner bacilli by extracts prepared from the fæces of patients suffering from dysentery. There is no further reference to copro-antibody until the paper published by Predpechensky and Moroz. in 1940. Between 1940 and 1944, however, there are at least seven further papers by various Russian workers, on copro-antibody. They confirmed the observations of Davis in further studies on patients suffering from dysentery.

Summarizing this work it would appear that the presence of copro-antibodies is considered to be of diagnostic value. Typical of the results obtained were those of Predpechensky and Moroz. Using the Shiga and Flexner strains as one antigen and a Strong and Sonne and a Schmitz strain as a second, 73 positive fæcal extracts were detected out of 90 patients suffering from dysentery. Bacteriological examination on the other hand revealed only 29 positives; however, when positive agglutination was accompanied by positive bacteriological examination, in most cases the two results were in concurrence with regard to the type of infecting organisms. Fæcal extracts from 21 normal people, and from 12 suffering from other forms of gastro-intestinal disturbance, were all negative. This type of result was reported by Skochko in 1942, who also showed that with the lengthening of the duration of the disease, the possibility of obtaining positive cultures decreased, with a proportional increase in the percentage showing copro-antibodies.

All these authors, including Davis, commented on the early appearance of copro-antibody, in many instances some time before the detection of serum agglutinins. In fact, Yampolsky *et al.* (1944) reported the presence of specific antibodies against the Flexner-Hiss organism on the first day of the clinical disease.

Barksdale and Ghoda (1951*a*, *b*) and Barksdale, Ghoda and Okabe (1951), though also noting the earlier appearance and disappearance of copro-antibody compared with serum antibody, questioned the specificity of many reactions, particularly with the different Shigella antigens and certain coliform organisms. The development of agglutinins against *Salmonella Spp.* and *Bact. coli* was also observed; this was considered to be an anamnestic reaction. Further experimental work on the development of copro-antibodies in rabbits gave considerable support to this hypothesis.

Ghoda (1952) suggests some caution therefore in the interpretation of copro-agglutination results when used for diagnostic purposes.

Burrows and his co-workers (Burrows, Elliott and Havens, 1947; Burrows, Mather, Elliott and Havens, 1947; Burrows and Havens, 1948) and Koshland and Burrows (1950) carried out extensive studies on the development of copro-antibodies against *Vibrio cholerae* in guinea-pigs. Copro-antibodies were well developed by the third day of infection, reached a maximum, and declined earlier than similar changes in the serum titre. There was a considerable influence on the infection by copro-antibodies, but not by specific serum antibody.

The stimulation of copro-antibody by the parenteral injection of vaccine ruled out bowel damage by the antigen as the means of passage of antibody to the lumen. Burrows and his colleagues concluded that because globulin was detectable in normal fæces the secretion or excretion of globulin was a normal function of the intestinal mucosa, which in response to antigenic stimulation modified the globulin in part to a specific antibody.

Burrows, Elliott and Havens (1947) also noted an anamnestic response in copro-antibody, and the presence of specific antibody in the urine of guinea-pigs concomitantly with fæcal antibody (Burrows and Havens, 1948).

Human volunteers actively immunized by the mouth or parenterally with cholera vaccine, developed specific fæcal and urinary antibody (urinary globulin is excreted at the rate of 8–17 mg. per day) which was again independent of serum antibody and had often reached its peak and was declining while the serum titre was still rising (Burrows and Havens, 1948).

The general conclusion of these workers is that fæcal antibody behaves independently of serum antibody and therefore is not derived from it.

Specific antiviral immune bodies in bronchial mucin were first identified by Francis (1940, 1943); Fazekas de St. Groth (1951), Fazekas de St. Groth and Donnelley (1950) and Fazekas de St. Groth, Donnelley and Graham (1951) confirmed Francis' observations emphasizing the role of antibodies in mucin as the most important determinant of specific resistance to influenza. Free antibody appears in the bronchial mucin at the same time as in the circulation, and its increase, climax, and decrease run parallel to that of serum antibody. This is in contrast to the copro-antibodies. However, the ratio of the antibody in bronchial mucin to serum antibody was twelve times greater when the antigen was administered into the respiratory tract than when the injections were intraperitoneal or subcutaneous. This may be related to the increased permeability of the tissues or capillaries of the bronchi following inflammatory changes produced by the local application of antigen.

This view was strengthened by further work which showed that mild inflammatory changes in the bronchi produced by the intra-nasal instillation of agents unrelated antigenically to influenza virus increased the local concentration of influenza virus antibody in the bronchial mucus (Fazekas de St. Groth, 1951).

Antibodies which have been detected in mucin derived from the bovine vagina and uterus are of veterinary interest. They are now widely used for the diagnosis of certain diseases of the reproductive tract namely trichomoniasis and vibriosis.

Many of the observations on copro-antibody also apply to vaginal antibody. The early development of agglutinins in vaginal mucin to *T. fœtus* is usual, and the absence of the naturally occurring agglutinin, present in all adult bovine serum has enabled the mucin agglutination test to be applied more effectively than the serum agglutination test for the diagnosis of the disease (Pierce, 1947). In terms of positive reactions the mucin test is at least four times more effective than the blood agglutination test (Pierce, 1949*a*, *b*). The independence of mucin and blood titres was noted by Stengenga and Terpstra (1949) and Lawson (1953) in *V. fœtus* infections.

Kerr and Robertson (1947) while confirming the occurrence of specific vaginal antibody to *T. fœtus*, also detected specific antibody in uterine secretions. From the point of view of antibody production the uterus and vagina appear to function as separate organs. Antibodies capable of immobilizing the trichomonad at a 1/80 dilution may be present in the vagina while infection persists in the uterus alone. These organs therefore develop antibodies not only independently of the serum but independently of each other.

In our further investigation of this aspect we have been fortunate with vaginal antibodies in that the active infection of the vagina with *T. fœtus* produces local antibodies in the mucin often without detectable circulating antibodies, whereas the stimulation of a high concentration of specific serum antibodies by the intramuscular injection of dead *T. fœtus* vaccine, unlike the copro-antibody as observed by Burrows, does *not* result in detectable antibody in vaginal mucin. In these circumstances, therefore, circulating antibodies stimulated by intramuscular injection of dead antigen do not pass into the vaginal mucin secretions. Kerr and Robertson have also shown this to hold true for the uterus and have been able to show that whereas antibodies stimulated by intramuscular injections are not found in uterine mucin, the injection into the lumen of the uterus of dead *T. fœtus* antigen will, as in the natural infection, provoke the development of local specific agglutinins in the mucin; circulating serum antibodies may under these conditions also be stimulated.

Several herds of cattle have been tested in which the two infections trichomoniasis and brucellosi

have co-existed. Only where the serum titre to brucella was particularly high (1/1280) was any trace of brucella antibody detectable in the vaginal mucin despite the presence of well-developed agglutinins in the mucus to trichomonas (Pierce, 1949*a*) and it is our opinion that damage to the vaginal wall by the introduction of vaccine or by active infection is not a factor facilitating the passage of antibody from the circulatory system into the mucin in the vaginal cavity. Local antibodies, therefore, detected in the mucus derived from the gut, bronchi, or reproductive tract may confer an immunity, particularly to localized infections of these organs, which may be far more effective than that depending on a high level of circulating antibody.

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Dr. H. Smith (Microbiological Research Department, Porton, nr. Salisbury, Wilts.): *Factors Involved in the Virulence-enhancing Action of Mucin.*

Nungester *et al.* (1932) discovered that a marked increase in the virulence for mice of strains of *Staph. aureus*, *Str. pneumoniæ* (Type II) and *Str. hæmolyticus* could be effected by injecting intraperitoneally a suspension of the organisms in 5% (w/v) commercial hog gastric mucin. About the same time Miller (1933) found that the same procedure would reduce the minimum lethal dose for mice of strains of *Neisseria meningitidis*. This so-called "virulence-enhancing action of mucin" has been used extensively for the production of many experimental infections in several different test animals (review: Olitzki, 1948). Most workers have used dried commercial hog gastric mucin, mainly but not solely the "Granular Mucin 1701W" of Wilson Laboratories, Chicago, U.S.A.

Although the term "virulence-enhancing action" has been used by the author, such a name for this effect is misleading. It implies an action on the organism, whereas it is known that the above preparations act by interfering with the host defence mechanisms; "the resistance lowering effect" and "the infection promoting effect" (Lambert and Richley, 1952) are better terms. Furthermore, the word "mucin" (or mucus) applies strictly to the viscous material coating mucous surfaces and secreted by the glands in those surfaces. Commercial preparations used to produce this effect are made by allowing the whole hog gastric mucosal tissue to autolyse, and then precipitating with alcohol. They certainly contain some of the constituents of the mucous coating the tissue, but other materials are undoubtedly present. The suspensions of these preparations are as viscous as native mucin, but they contain far more insoluble material. This paper will describe briefly the identification of the factors which are involved in virulence enhancement in this type of preparation, and the repercussion of this purely chemical work on research into their mode of action. Finally, the biological activity of more natural "mucins" will be noted, and the role of mucin in the pathogenesis of mucosal infections discussed.

Factors Involved in the Virulence-enhancing Effect of Preparations from Whole Hog Gastric Mucosal Tissue

Chemical extraction of fresh hog gastric mucosæ and identification of the factors responsible for virulence-enhancing activity proceeded in four main stages.

(*a*) *Assay of fractionation samples for virulence-enhancing activity* (Smith, 1950*a*). The system

for detecting the activity has been an intraperitoneal injection of the sample with 5,000 *Salmonella typhosa* into large batches of mice. Adequate controls ruled out toxicity, and any deaths indicated an enhancement of virulence of 1,000 times, since 5×10^6 is the normal LD_{50} for the strain of *Salm. typhosa* used. Samples were assayed by comparing (by probit analysis) the death-rates for various concentrations of the material under test, with those produced by a "standard" preparation.

(*b*) ***Proof that the virulence-enhancing activity was not due to one single factor, but to a synergic combination of three factors.*** Two of these were reasonably non-specific—a viscous medium and particulate insoluble matter—and one which was specific, the "third factor" (Smith, 1950*b*, 1951*a*; Smith *et al.*, 1951). Table I shows in schematic form the chemical fractionation up to the separation of these three factors. Turning first to the "viscosity factor" and "residue factor", the result of virulence enhancement experiments (Smith *et al.*, 1951) on these factors isolated from hog gastric mucosæ and on other viscous and insoluble materials, showed that at high viscosities (10 times that in Table II) and high concentrations of insoluble materials (3 - 4 times those in Table II) both factors had biological activity if injected alone, and that the effect was non-specific. Table II shows the results of similar experiments in which viscosities, and concentrations of insoluble materials, which were ineffective alone, became highly virulence-enhancing when combined. At this stage of purification the "third factor" gave some activity when injected alone at 1% w/v concentration. In the presence of a mixture of particulate residue and a viscous medium, the concentrations of which were reduced so that they were inactive alone, only 0·05% w/v of the "third factor" was needed to manifest activity.

TABLE I.—CHEMICAL EXTRACTION OF HOG GASTRIC MUCOSÆ UP TO THE SEPARATION OF VISCOUS CONSTITUENTS, INSOLUBLE RESIDUE AND "THIRD FACTOR"

Fresh hog gastric mucosæ
↓
Minced, autolysed 1 week, 37° C., pH 3
↓
Autolysate precipitated with 4 vols. alcohol
↓
Dried by stirring with fresh alcohol
↓
Defatted by washing with trichlorethylene
↓
Dry solid extracted with water at pH 4·3–4·5

↓ Residue	↓ Solution of viscous constituents *Viscosity factor*
↓ Extracted with $NaHCO_3$ at 37° C.	
↓ Insoluble residue *Residue factor*	↓ Solution "*Third factor*"

TABLE II.—THE EFFECT OF A COMBINATION OF INSOLUBLE PARTICULATE MATTER AND A VISCOUS MEDIUM IN ENHANCING THE VIRULENCE OF *Salmonella Typhosa* FOR MICE

(Figures are death-rates %, in batches of 20 mice, produced by the material under test with 5,000 *Salmonella typhosa*)

Material producing media of equal viscosity (approx. 8 times that of water)	Insoluble particulate matter					
	Nil	Residue from hog gastric mucin 1·5%	Charcoal 2·5%	Kaolin 2·5%	Fuller's earth 2·5%	Talc 5%
Nil	—	0	0	0	0	0
Viscous material from hog gastric mucin 1·75%	0	90	100	65	65	30
Tragacanth 0·12%	0	45	55	45	50	55
Acacia 10%	0	60	95	30	40	20
Agar 0·16%	0	55	80	70	80	60
Cellofas 0·4%	0	45	95	25	20	55

(*c*) ***Fractionation of the "third factor"; and proof that heparin and two other carbohydrate components were responsible for the activity*** (Smith, Gallop and Stanley, 1952; Smith, Gallop, Harris-Smith and Stanley, 1952; Smith and Gallop, 1953; Smith, Zwartouw, Gallop and Harris-Smith, 1953). A biological assay was used in which experimental samples and a "standard" sample were

injected in the presence of an inactive mixture of 0·4% w/v charcoal, and tragacanth mucilage of constant viscosity (Smith *et al.*, 1951). A description of this complex fractionation, using mainly barium acetate and ethanol cannot be given here. Table III shows the four carbohydrate components each of which was electrophoretically and ultracentrifugally homogeneous. The virulence-enhancing activities compared with the "standard" sample of activity, 1 virulence-enhancing unit per gramme, are also included; the most probable figure is given with fiducial limits (P = 0·95) in brackets. It is evident that a heparin was the most active component. This was adequately checked; the sample was crystallized and complied exactly with the analysis of heparin; commercial samples of heparin were active, and so was a specially purified sample of heparin, kindly supplied by Dr. F. Bergel of Roche Products Ltd. The activity of polysaccharide C was not connected with either its blood group A or H character; two samples having relative blood group A activity 500 – 1 and H activity $\frac{1}{32}$ – 1 had virulence-enhancing activities of 1·2 (0·9–1·6) and 1·1 (0·8–1·4) virulence-enhancing units per gramme respectively. Polysaccharide B had negligible activity.

TABLE III.—NATURE AND RELATIVE VIRULENCE-ENHANCING ACTIVITY OF COMPONENTS OF THE CARBOHYDRATE FRACTION OF THE "THIRD FACTOR"

(Assayed in the presence of a constant amount of charcoal in a tragacanth medium of standard viscosity)

Polysaccharide	Nature	Activity (virulence-enhancing units/gramme)
A	A heparin (mucoitin disulphuric acid)	3·9 (2·9–5·1)
B	Contains acetylchondrosamine sulphuric acid, and probably d-glucuronic acid	0·5 (0·3–0·7)
C	The blood group mucoid of Morgan and King (1943) and Bendich *et al.* (1946)	1·1 (0·8–1·4)
D	A chondroitin-sulphuric acid	1·0 (0·8–1·2)

(*d*) *Reconstitution of an active "mucin" step by step from the main factors operating in this complex system.* Table IV summarizes the results of these experiments. A solution (1·5% w/v) of polysaccharide C, i.e. a weakly active component of the "third factor", had a viscosity equal to that used in all our experiments (approx. 8 times that of water), and hence supplied the "viscosity factor". If injected alone, in the system already outlined, practically no deaths were apparent. As particulate residue, polysaccharide A (heparin) and polysaccharide D (chondroitin-sulphuric acid) were added, significant increases in death-rates were observed, and the final mixture was powerfully virulence enhancing.

TABLE IV.—RECONSTITUTION OF AN ACTIVE "MUCIN" BY COMBINING THE MAIN FACTORS INVOLVED IN VIRULENCE ENHANCEMENT

(Adequate controls ruled out toxicity)

Nature of injection solution: Material	Conc. %w/v	Deaths in batches of 50 mice when injected with 5,000 *Salmonella typhosa*: Expt. 1	Expt. 2	Expt. 3
1. Polysaccharide C	1·5	0	2	2
2. Polysaccharide C	1·5	11	7	12
Particulate residue	0·25			
3. Polysaccharide C	1·5			
Particulate residue	0·25	30	21	24
Polysaccharide A	0·05			
4. Polysaccharide C	1·5			
Particulate residue	0·25			
Polysaccharide A	0·05	—	38	29
Polysaccharide D	0·1			

Repercussion of This Chemical Work on Research into the Mode of Action of These Preparations

Chemical fractionation has shown that biological activity is due to a complex system of interacting factors. It is thought, therefore, that the overall activity of mucin is due to a combination of different biological properties, and this complex problem should be approached by an investigation of the properties of the individual factors, before an attempt is made to use a combination of them. In other words, it would be better to stop using the crude preparation which most workers have used up to the present (Olitzki, 1948) and to work, at first, with components. A former colleague, Dr. H. P. Lambert (Lambert and Richley, 1952) has started work in this direction by investigating certain biological properties of heparin in relation to this problem, particularly the anticomplementary and antiphagocytic properties.

The Virulence-enhancing Activity of Other "Mucins"; the Role (If Any) of Mucin in the Pathogenesis of Mucosal Infections

Table V gives a list of different "mucin" preparations which were virulence-enhancing in the test described above. The samples examined by Smith (1951*b*) were freeze dried and redissolved at known concentrations before test. It is unlikely that any artefact could appear in this treatment, but the author is unaware of any experiment in which a mucin was obtained directly from the mucous surface and tested for virulence enhancement immediately, without prior treatment of any kind.

TABLE V.—VARIOUS MUCINS AND MUCOSAL EXTRACTS SHOWN TO HAVE VIRULENCE-ENHANCING ACTIVITY

Activity Reported in the Literature (*Olitzki*, 1948)

Human gastric mucin
Human salivary mucin
Hog gastric mucin
Hog intestinal mucin
Guinea-pig intestinal mucin

Examined by Smith (1951*b*) *and Found Active*

Human salivary mucin
Human stomach mucosal extract
Human small intestine mucosal extract
Human large intestine mucosal extract
Human respiratory mucin (bronchiectasis)
Human nasal mucin
Human umbilical cord mucin
Human pseudomucinous ovarian cyst mucin
Hog gastric mucus

Apart from the results of trauma, practically all pathogenic infection takes place on and across mucous membranes. It is surprising, therefore, that so little research has been carried out on the functions in this attack of mucins which cover these surfaces. It may well be that mucins have no marked effect on the course of the infection, but this has yet to be proved or disproved. Extension of the classical function of lubrication and mechanical protection of epithelial surfaces to antibacterial protection is readily assumed and there is evidence for this (Goldsworthy and Florey, 1930). The mechanical removal of particles by a continuous secretion of mucin and its movement by the ciliated epithelium on some surfaces seem to be the main protective mechanism. If, for some reason, this movement of mucin stops, the biological activity of mucins described above may help pathogens to attack mucous surfaces. This, however, remains a speculation. The activity of the various "mucins" when injected intraperitoneally in the completely artificial mouse test described above may not be apparent in tests involving a more natural infection on a mucous surface. It is true that Hill, Huffer and Nell (1945) have found that *Neisseria gonorrhoeæ* survive far longer on the mouse vaginal surface when suspended in hog gastric "mucin", than when suspended in saline, and the use of hog gastric "mucin" for the production of pneumonias by intratracheal instillation is a well-established procedure (Olitzki, 1948). However, no large-scale experiments on more natural infection of mucosal surfaces by pathogens suspended in the mucin from the appropriate mucosa, have ever been carried out. Elucidation of the role of mucin in the pathogenesis of mucosal infections must await the results of such experiments.

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DISCUSSION ON ORGANIC MANURES AND FERTILIZERS AND THE PRODUCTION AND COMPOSITION OF FOOD FOR MAN AND ANIMALS

Sir William G. Ogg (Director, Rothamsted Experimental Station): *The Present Position.*

It has been recognized from very early times that, on most types of land, manures must be applied if satisfactory agricultural crops are to be grown. We find references to manuring in Chinese, Egyptian, Greek and Roman literature and it is practised by even primitive tribes.

In order to maintain or increase fertility it has been the practice in most parts of the world to return to the soil crop residues, animal manure and domestic waste and to rest the land for periods under grass. If production is not too intensive, this system is generally successful provided there is not a natural deficiency of some essential mineral nutrient. Liming has long been practised and in the early part of last century such materials as ground bones and guano were used to a limited extent. About the same time the nitrate of soda deposits of Chile were discovered and ammonium salts began to be produced as by-products of industry but there was very little knowledge either of the needs for these substances or of how they should be used.

The Introduction of Fertilizers

That was the position when John Bennet Lawes, the young squire of Rothamsted, began the famous experiments which resulted in his taking out a patent in 1842 for the manufacture of a water-soluble phosphatic fertilizer, superphosphate, which gave a quicker and better response than bones. Although Lawes became a chemical manufacturer, his main interest was in agricultural experimentation and, over the next half-century, he and Gilbert laid the foundations of our knowledge of crop nutrition. They studied the manurial requirements of different crops, compared the new fertilizers with farmyard manure and demonstrated that crops could be grown over long periods with fertilizers only without loss of yield. The pioneer work of Lawes and Gilbert has been supplemented and expanded by experiments in most parts of the world and there is now a fairly good understanding of the principles of manuring and of the manurial requirements not only of different crops but of different classes of soils.

The introduction of fertilizers came at a most opportune time. Changes in our social and sanitary habits and the very great increase in population not only in this country but throughout the world have raised new problems in food production. With the concentration of population in great cities and with modern systems of sanitation, much of the manurial residue which used to find its way back to the land is now carried as sewage to the sea. Fertilizers have enabled the farmer to make good the losses and also to increase production. They have not superseded farmyard manure which, in addition to its manurial value, has important physical effects on the soil, but they are a source of additional plant food and without them the present population of the world could not be fed.

The Inadequate Supplies of Organic Manure

The total amount of farmyard manure produced annually in England and Wales is estimated at about 35,000,000 tons which provides little more than a ton per arable acre per annum in eastern England and 2–3 tons in most other parts of the country, apart from intensive dairying districts where it is 5–6 tons. Part of the plant food in farmyard manure is available only over a long period of years and it is difficult to give its exact fertilizer equivalent. From field experiments, however, it has been estimated that in terms of readily available nutrients the farmyard manure made annually in this country provides only about a third of the amount of nitrogen, a quarter of the phosphate and half the potash applied in the form of fertilizers. Before the war we imported large quantities of animal feeding stuffs, the manurial residues of which made a very substantial contribution to the fertility of our soils. This has been reduced to about half and the balance must be made good by fertilizers.

There are other potential sources of organic manures in the form of town refuse, sewage sludge and various other waste materials. Of these, sewage sludges are the most promising but they are of less value than good farmyard manure. As they are bulky, their use is restricted to the areas to which it is economic to transport them and they are of more interest to market gardeners than to farmers.

It is clear that farmyard manure supplemented by all the organic waste materials available cannot provide the necessary nutrients for present-day agriculture in this country and the same is true in the United States. An American Congress Report (No. 3254 Union Calendar No. 1139, January 1951) on the use of chemicals in food products, states that "The supply of organic matter which could be used for fertilization purposes, however, would furnish only a small fraction of the need for fertilizers now being met by the use of commercial fertilizers". In the same report there is the following statement by Dr. Emil Truog, one of the leading authorities on soil fertility in the United States: "Fortunately

this country has large supplies of the raw materials for the manufacture of the needed chemical fertilizers without which a continuing highly productive and prosperous agriculture would be impossible. The raw materials existing largely as deposits of phosphate rock, potash salts and sulphur, should be conserved as far as possible for posterity by making all possible use of sewage, garbage and other waste materials for fertilizer purposes. However, in this connexion it is important to recognize that, if all of the readily available garbage and organic wastes produced in this country were turned into compost as proposed by the adherents of the organic school, the total production would probably not provide more than 5 to 10% of the fertilizer elements needed to keep our soils in a satisfactory state of production."

Fertilizers and Increased Food Production

It is, of course, possible to maintain reasonable crop yields for many years without the use of fertilizers by cashing in on the natural fertility of the land and on the residues of previous applications of farmyard manure and fertilizers but this could not be done indefinitely with intensive cropping. It has sometimes been suggested that special crops should be grown for the purpose of making compost but the production, handling and application of farmyard manure as a by-product is not by any means cheap and to set about growing crops for the sole purpose of converting them into manure would be prohibitive in both land and labour. Besides, we must recognize that there are many regions where there are actual deficiencies in certain plant foods—natural shortages of phosphate, potash or trace elements—and the dung or compost prepared from such land will have the same deficiencies. The application of fertilizers and trace elements has enabled large areas in many parts of the world, which were formerly waste, to be brought under cultivation.

Much of the increase in food production in Britain during and since the war is the result of using more lime and fertilizers and using them more effectively. Before the war, we were relatively modest users compared with certain European countries with roughly similar climates and systems of farming. Holland used five times, Belgium three times and Germany twice as much fertilizer per arable acre as we did. Since then fertilizer consumption has been practically trebled both in this country and the United States; the arable acreage has at the same time been increased but we are using much more fertilizer than before the war.

Surveys of Fertilizer Practice recently carried out by Rothamsted in conjunction with the National Agricultural Advisory Service indicate, however, that many farmers are still using inadequate amounts and that food production could be substantially increased by using more.

The Anti-fertilizer School

Attempts have been made to create a controversy over the respective merits of organic manures and fertilizers. The conflict of opinion is, in fact, between those who advocate the proper use of both and a very small minority who oppose the use of fertilizers. Neither farmers nor agricultural scientists decry the value of organic manures nor claim that fertilizers can fulfil all their functions. As well as improving the physical conditions of soils they are a valuable source of nutrients not only to the crops but to the soil organisms and they help to retain the nutrients added as fertilizers. The amount of organic manures is, as we have seen, however, quite inadequate for the needs of present-day agriculture.

Those opposed to the use of fertilizers allege that they are detrimental to soils, crops, animals and human beings, but most of the ills attributed to them existed before these materials were discovered and are rife where they have never been used. There are several schools of thought, but most of them share the belief that there is some vital principle which must be passed on in the form of plant or animal manure if our crops and even we ourselves are to thrive. This is merely a hypothesis and so far no adequate scientific data have been brought forward to support it. There is, in fact, evidence from hydroponics that crops can be grown satisfactorily in the complete absence of organic matter. There could be no objection, however, to the "vital principle" theory if those who held it did not at the same time condemn fertilizers.

There are various degrees of dislike amongst those who oppose the use of these materials. Some will admit burnt lime or ground rock phosphate as natural manures and others would allow the use of basic slag but would refuse to accept superphosphate, sulphate of ammonia and potash salts. Then there are those who not only reject fertilizers but follow rituals recalling the magical practices of the alchemists. It often appears to be a question of dislike to chemicals but such antipathies are a poor basis for a policy of land fertility. Much use is made of such expressions as "the living soil" and biological soil studies are extolled whilst those connected with chemistry are disparaged, but the pioneer work on soil micro-organisms was not done by the anthroposophists but by Robert Warington at Rothamsted between 1877 and 1890.

Fertilizers and the Soil

Let us examine some of the alleged harmful effects of fertilizers on the soil. It is often stated that those who use fertilizers are exploiting the fertility of their land and using up its organic matter, thereby damaging its physical condition and causing erosion. The reverse is the case. By enabling

larger crops to be grown, fertilizers increase the amount of material which can be converted into manure and the greater amount of roots and stubble left by the bigger crops also increases the organic matter in the soil. This has been shown on Broadbalk field at Rothamsted. There is no evidence that erosion is associated with the use of fertilizers. In the Dust Bowl of America the annual consumption of fertilizers was only about 1 cwt. sulphate of ammonia, 15 cwt. superphosphate and 0·5 cwt. muriate of potash per thousand acres of crop and the erosion was due to too frequent ploughing.

At Rothamsted, where for experimental purposes, soils have received very heavy annual dressings of fertilizers for over a century, good yields have been maintained and the soils are still in excellent condition. Careful investigations have shown that no harm has been done to the bacteria and other micro-organisms. The number of soil organisms can be increased by adding organic matter, but a mere increase in numbers is not necessarily beneficial. Indeed, during the decomposition of organic matter rich in carbohydrates the micro-organisms may make heavy demands on plant nutrients, especially nitrogen, and compete with, and temporarily starve, the crop. It has been claimed that fertilizers reduce the earthworm population but this is not borne out by the work at Rothamsted even on soils which have received long-continued and heavy dressings of fertilizers, provided the soil has not been allowed to become too acid. It is, of course, well known that sulphate of ammonia increases the rate at which lime is leached from the soil and this in time leads to acidity, but it can be readily corrected by liming.

Fertilizers and the Crops

It is recognized that fertilizers must be used properly and in the correct form and amount to suit the needs of the soil and the crop. Most of them provide plant nutrients in a concentrated and rapidly available form and one or more nutrients can be selected at will to meet a special need or make good a deficiency. This flexibility in use renders it easier to make mistakes and an unsuitable balance of nutrients may adversely affect the yield and composition of the crop. Most organic manures on the other hand release their nutrients more slowly and over a long period and their use is relatively safe even in inexperienced hands. They usually contain most of the necessary plant food elements but often in unsuitable proportions for the particular soil or crop and fertilizers have a special value in correcting the balance. Organic manures and fertilizers are complementary and in good farming practice both are employed.

It is sometimes alleged that fertilizers increase the liability of crops to suffer from disease and that they have adverse effects on the composition and food value of the produce. But work at Rothamsted and elsewhere has shown that nitrogenous fertilizers can be used to stimulate crops so that they can withstand attacks of such diseases and pests of cereals as Eye-spot (*Cercosporella herpotrichoides*), Take-all (*Ophiobolus graminis*) and wheat bulb fly (*Leptohylomyia coarctata*). Various factors, including manuring, can influence composition but there is no evidence from the Rothamsted experiments that organic manures have any special effect, beneficial or otherwise, compared with properly balanced fertilizers.

It would appear that in America the war has been carried into the other camp and equally sweeping claims made on behalf of fertilizers. A Committee of the House of Representatives has recently reported on the use of fertilizers and the following paragraph sums up the position:

"The unsubstantiated charges that the use of chemical fertilizers is causing many serious diseases is matched by the equally undemonstrated claims that the employment of chemical fertilizers has resulted in increased longevity and decreased dental caries among other things. The present status of knowledge in this general field calls on the one hand for the curtailment of enthusiasm based on inadequate data or on speculation as to the alleged direct bearing of soil fertility on health. There is a real need on the other hand for carefully controlled long-term studies to determine what relationships, if any, actually exist."

Dr. **G. C. Ainsworth** (University College of the South West, Exeter): *The Relationship to the Growth and Health of Plants.*

Man has always been impressed by catastrophe and it is instructive to trace his changing views on disease in plants. In Biblical times plant disease was attributed to the Almighty, in the Middle Ages the Devil—the evil eye—was held to be responsible, while by the early nineteenth century the weather was being offered as one explanation of the devastating outbreaks of potato blight which caused the Irish famine. It was the widespread interest in potato blight that led an English country clergyman to discover the pathogen and for the next hundred years disease in plants, as in animals, was dominated by the pathogen. Recently, increasing appreciation is being shown of the fact that disease results from the complex interaction of many factors: the plant, the pathogen, the physical environment, and even the prevailing social and economic systems; an outbreak of disease may be determined by the size of a grower's overdraft at the bank. And the same complex situation determines the health of plants, for disease is only a deviation from the standard which we call health.

In this discussion certain selected aspects of the total situation are under consideration, and, in particular, the soil-plant interaction, but even this simplification leaves a very complicated residue,

for the soil is a microcosm in which there are many factors interacting with one another and with the growing plant. In spite of centuries of empirical experiments on the cultivation of plants, a hundred years or so of the application of scientific methods to agricultural and horticultural practice, and a few decades of intensive soil microbiology there is still much to learn about the fundamental processes involved. As a botanist and a microbiologist, I shall attempt to indicate the broad pattern of this soil-plant system and how it is affected by the use of organic manures and chemical fertilizers.

The Soil-plant Interaction under Natural Conditions

Some higher plants are able to dispense with soil and the recent development of "soil-less culture", the large scale adaptation of laboratory water culture techniques, is well known. Many plants can be well grown by soil-less culture and the method provides a clue which leads a botanist to the permanent natural demonstrations of the origin of a soil provided by coastal sand dunes. There, on the landward side dune, high-tide mark is bare sand which microbiological examination shows to be supporting small numbers of bacteria but no fungi. As the fore dune is ascended marram grass (*Ammophila arenaria*) typically becomes dominant, microscopic fungi can be demonstrated in the underlying sand which contains fewer bacteria, whilst, in season, the fruit bodies of several species of larger fungi may be observed. As the semi-fixed dune gives way to fixed dune and the vegetation becomes more luxuriant the marram grass grows less and less vigorously and dies out long before the climax grassland, or under acid conditions heathland, is attained, and this in spite of the fact that marram will grow well when planted alone in a garden soil. This series of changes which can be traversed by a few minutes' walk illustrates with the minimum of complication some of the characteristics of soils and their associated vegetation. The main features from the point of view of this discussion are the constant association of a particular plant or plants with a particular type of soil—position on the dune can be ascertained merely by looking at the ground—the increasing diversity and luxuriance of the vegetation and the soil microflora as one proceeds from soils of low to those of high organic content, and the changing relation of the fungi to the higher plants; on the fore dune the fungi are probably mostly, if not all, saprophytic or parasitic while the association (the so-called mycorrhiza) between such plants as ling (*Calluna vulgaris*) and pine trees and specific fungi on the heathland is mutually obligatory for the development of both partners.

The Soil-plant Interaction under Cultivation

On cultivated land man grows such crops as he will (or such as experience has taught him can be profitably grown) and he usually grows, not an association of different plants, but extensive pure cultures very different from the natural climax vegetation of the particular region. Further, at intervals he removes the crop. Green plants are not dependent on the soil for their carbon but they are dependent on the soil for their other nutrients. Under natural conditions plants die and decay in situ and so repay their debt to the soil, together with interest in the form of organic matter. Under conditions of continuous cultivation the inevitable depletion of the soil must be made good. In primitive societies and in newly colonized, underpopulated regions the exhausted soil is abandoned, a new site is cultivated and the fertility of the exploited soil is slowly renewed by natural processes. In the more advanced and more densely populated countries this is not possible as there is no longer any virgin soil available. Under these conditions the use of chemical fertilizers is a convenient and satisfactory way of supplying the needed nitrogen, potassium, and phosphorus, that trinity of elements basic for plant growth, if there is a proper understanding of the requirements of the particular crops so that the application of the fertilizers is that appropriate for the rotation.

In addition to elements needed in relatively large amounts there is a series of elements which are essential for the growth of many if not all plants but only in exceedingly small amounts. Here again the use of chemicals is the rational procedure and the application of small quantities of boron, copper, or manganese, for example, may render an unsatisfactory soil fertile.

But an agricultural or horticultural soil has not the simplicity of a controlled and mechanically irrigated sand culture. The organic matter it contains plays a vital role in conserving moisture and in providing a substrate for the growth of micro-organisms which in their turn affect the physical condition of the soil by determining crumb structure and by making available materials which can be utilized by the higher plants. At the same time the microflora competes with the higher plants for nutriment and certain fungi, particularly those which are termed "soil invaders" as opposed to the "soil inhabitants", may cause disease in higher plants while, as already mentioned, another class, the mycorrhizal fungi, set up a symbiotic relationship with higher plants. The practice of combining animal husbandry with arable farming and the use of farmyard manure is the age-old solution to the problem of maintaining both the inorganic and the organic constituents of the soil and the microbial population which is essential for fertility; but the advent of the motor car and the tractor and the vast increase in the scale of farming have rendered this solution inadequate. New sources of organic manures such as composted crop residues and town refuse are having to be explored. It has been suggested to me that in this connexion the possibility should be borne in mind that the nitrogen, potassium, phosphorus and other elements in organic manures may be in a form more acceptable for plant growth than is the chemically equivalent amount in the form of inorganic fertilizers.

Sometimes it is necessary to ensure that the requisite symbiont for a particular plant is introduced into the soil when the plant is grown in a new situation. One of the simplest examples of such a procedure is the method developed at Rothamsted Experimental Station for the inoculation of lucerne seed with the specific strain of nodule-forming bacterium able to fix atmospheric nitrogen. The same problem may also arise in afforestation schemes but usually a sufficient inoculum of the appropriate mycorrhizal fungi is transferred to the new site from the nursery beds of forest soil on the roots of the young plants.

The Soil-plant Interaction and the Environment

The summation of the soil-plant interaction is made manifest by the response of the plant to weather and the pathogen. Perhaps the best test of a satisfactory soil is still the production of what an experienced grower recognizes intuitively as a "well-grown plant". A disbalance in the inorganic nutrients in the soil such as too heavy nitrogen manuring of cereals may result in soft growth and in "lodging" of the plants under weather conditions which would not affect correctly manured plants. In the same way soft lush growth may emphasize the effects of infection by a pathogen. There is no evidence that a well-grown susceptible crop plant is able to escape infection when the pathogen is present and the environmental conditions are favourable for its development. For many virus diseases the symptoms are most severe when the plant is growing well. On the other hand, a deficiency of potassium undoubtedly seems to favour the development of chocolate spot in broad beans (caused by the fungus *Botrytis cinerea*), attacks of which can be reduced in severity by the application of adequate potassium, to cite one example of a response to a chemical fertilizer, while experiments have shown that attacks of potato scab (caused by the actinomycete *Streptomyces scabies*) can be prevented by green manuring, that is by ploughing in a green crop such as mustard or by the application of grass cuttings. It has been suggested that the beneficial effect in this instance is due to the encouragement of the growth of saprophytic actinomycetes which compete with the pathogenic forms. Perhaps the production of antibiotics by the saprophytes plays a part. Evidence has been obtained that it is the production of antibiotics by soil penicillia that renders certain Wareham Heath soils unsuitable for the growth of the mycorrhizal fungi necessary for conifers. Antibiotics, or to generalize, antagonisms between micro-organisms, certainly play a part in the adjustments between different components of the soil microflora, and the discovery of the potentially very important use of systemic fungicides and insecticides in the control of diseases and pests suggests that plants may absorb such substances from the soil. Also, plants may obtain from the soil small amounts of vitamins or other complex organic compounds necessary for their complete nutrition.

Dr. D. P. Cuthbertson (Rowett Research Institute, Bucksburn, Aberdeenshire):

The use of fertilizers as an adjunct to organic manures permits replacement of the elements which have been removed in the course of the natural cycle in the farm unit concerned. No amount of composting can return to a farm the products which move out of it in the form of crops and livestock consumed at a distance, e.g. consider the distance involved in the Canadian wheat consumed in this country. The use of natural organic manures alone cannot supply the trace elements which are deficient over considerable areas of the world, for even if transported from non-deficient areas there would not be enough, and it is doubtful if there ever could be enough available for the purpose. I would instance the losses in stock due to deficiencies of copper, cobalt, zinc, iodine and phosphorus throughout the world. It is true to say that Australian agriculture for one would collapse without fertilizers.

We know that the effects of fertilizers on the mineral composition of plants are frequently indirect as well as direct: for example, the depression of the magnesium and calcium content of a crop caused by high dressings of potassium fertilizer. The effect may sometimes be large enough for the crop to suffer magnesium deficiency if growing on a soil rather low in magnesium and it is possible that this in turn may lead to a lower intake of magnesium by the animal, but the requirements of animals for magnesium are low. The tetany in cattle associated with hypomagnesæmia is obscure and can occur where the content in the fodder is apparently adequate.

The advocates for organic farming as a whole state that the full benefits of composting, the four-year ley and grazing as fertilizing agents are not achieved by orthodox farming, since the manure from livestock fed on concentrates will be deficient in certain essential minerals. I know of no evidence which permits such a generalization to be made, provided there is intelligent balancing of the fertilizers used along with farmyard manure, and provided the soil is not intrinsically deficient in some minerals and which are not thus made good.

As to the protein content of plants it is recognized that any manurial system which alters the proportion of the leafy, to stem and flowering parts of a plant, will affect the ratios of the individual proteins. It may also affect the concentration of free amino acids and non-protein bound amino acids. As the application of nitrogen fertilizers tends to delay the onset of maturity there will be corresponding changes in the proportions of these constituents but there is no evidence of any imbalance of amino acids or adverse effect on proteins arising from the use of fertilizers.

The evidence indicates that such effects of fertilizers on the vitamin content of crops as occur are relatively small and vary with the species of plant. For example, the accumulation of ascorbic acid in plants is characteristic of the species and variety and this genetic stability will outweigh any differences due to climate, soil or fertilization.

In some of the earlier experiments, particularly the oft-quoted experiments of McCarrison which hinted that the nutritional value of wheat and millet grown on land with cow dung and no other fertilizer was better as a source of B-vitamins, particularly vitamin B_1 for pigeons and rats, there appears to have been no replication of the experimental plots and only their mean effects are given. It is thus impossible to evaluate their significance in terms of modern statistical analysis. Subsequent work in India and elsewhere has failed to supply support to this aspect of McCarrison's work. It should be noted that in his 1924 paper McCarrison points out that as the result of financial retrenchments his research had to stop and that though the results are so consistent, he would not desire, in the absence of further work, to assert that they are to be regarded as final. As I have already pointed out, no overall support has been forthcoming from subsequent workers.

Let us turn now to the health records of man and his stock, particularly in those countries where there is a very considerable use made of chemical fertilizers and let us remember that normally man derives his foodstuffs from a variety of sources. It is acknowledged that two of the most sensitive indices of health of man about which there can be no dubiety are the infant mortality rate and the expectation of life. I find no indication that the increased use of chemical fertilizers has affected adversely the general decline in infant mortality or the increase in the expectation of life. For example, the health records of the Netherlands are certainly as good as those of France and this is compatible with a sixfold difference in fertilizer usage in favour of the Netherlands. Similarly the health records in the United Kingdom are as good as those of Ireland and this is compatible with a threefold difference in fertilizer usage in favour of the United Kingdom. Taking such criteria as the generally accepted public health standards, we find that the best health conditions which we can observe are compatible with the general consumption of foods grown on chemically manured soil. We are, however, only too conscious that the increase in duration of life is due in part to the control of acute infections by sulphonamides and antibiotics. At the same time we recognize that for the same reason there is an apparent increased incidence of the remaining killing diseases with age. This apparent increase is also due, in part, to improved diagnostic techniques. As each killing disease disappears the incidence of the remaining diseases is likely to increase as the continually ageing organism becomes less and less able to combat them. Having stated this, we also recognize that certain degenerative diseases like disease of the coronary arteries which occurs at earlier ages seem definitely on the increase. Why, we do not yet know.

We are not blind to the fact that with the use of chemical fertilizers goes industrial and economic development which in turn go with good sanitary conditions, and a low infant mortality rate and high expectation of life. It is, of course, arguable that the health picture of China and similar countries would be even worse if artificial manures were substituted for the organic manures which they use, all other factors being kept constant. But, since it is impossible in any case to compare countries that differ in almost every detail of diet and hygiene, that refinement of speculation appears profitless.

Turning to farm animals, we note that there has been over the past few years an uneasiness amongst some farmers and veterinary practitioners that some of the so-called metabolic diseases of cattle, e.g. acetonæmia, lactation tetany and bloat, and enterotoxæmia in sheep—which appear to them to be on the increase—are associated with the increased production of grass, particularly through the use of chemical fertilizers by keen farmers. It has also been hinted that the farms chiefly afflicted are those with high-yielding herds. But the general improvement in the standard of farming has also made the keen men more disease conscious.

It is obvious that grassland improvement must be assessed by its effect on the grazing animal and that careful pasture and stock management may be necessary to ensure that some of the ill-effects which have been observed are controlled. A search of the literature by Dr. Russell Greig and his colleagues at the Animal Diseases Research Association and the Veterinary Investigation Officers in Scotland has given no definite evidence that the improvement in grassland management has materially affected the health of grazing animals. Unfortunately the literature on the subject deals far too much with nebulous statements and hypotheses that have, so far, no substantiation in accepted scientific fact, and the stockowner is becoming stampeded into thinking that his attempts to run his farm efficiently with an increasing production are having alarming results on his stock. It is suggested that since the major infective scourges of the dairy cow—e.g. contagious abortion, mastitis and even tuberculosis can now be largely rationally controlled, diseases like acetonæmia and lactation tetany, which were formerly considered as of relatively minor importance, are now regarded as of relatively major importance. Improved methods of diagnosis and advances in rational treatment have thus made farmers more disease conscious. There are many farms on which improvements in grassland management have been carried out and on which there has been no increase in the incidence of disease of the grazing animals. Finally, in the light of the paucity of exact knowledge at the moment we should give no publicity to any hypothesis or suggestion which would deter the agriculturalist from trying

to obtain the maximum yield per acre or from continuing the grassland improvement demanded by the present economic conditions. I would mention that on the farm of the Hannah Dairy Research Institute a considerable scale of fertilizer application has been used, in addition to all the dung produced on the farm and this has, as on most farms, been the practice for many years. Its Director, Dr. J. A. B. Smith, has assured me that he has been unable to note any measurable ill-effect on the soil, the quality of the crops or on the animals themselves.

Study of the causes and control of the spectacular infertility disease which appeared suddenly in Australia in 1941 and seriously affected the sheep-raising industry over 8,000 square miles has progressed. The subterranean clover seriously disturbs the hormone balance of the female and castrated sheep, but not the rams. Although a remedy for sheep affected by the disease is not yet possible or probably cannot even be expected, nevertheless one of the best control measures found to reduce this clover is the use of superphosphate as a fertilizer to stimulate other plants.

In conclusion I have found no real grounds for uneasiness but it is always wise to be vigilant and on the first serious suggestion of anything being wrong to investigate thoroughly. At the moment, too many people die through insufficient food: the balanced use of fertilizers could do much to offset this if coupled with good husbandry both plant and animal.

Sir James Scott-Watson (Ministry of Agriculture):

Our present body of knowledge about soil fertility, soil conservation and soil improvement is, in part, the product of farming experience accumulated over a period of some eight thousand years; in part, also, it is the product of scientific investigation during recent times. It is barely a century since the broad principles of plant nutrition were established.

In general, traditional measures for soil conservation and soil amelioration are effective in the area for which they have been devised. But a given system may completely fail when applied under different soil and climatic conditions. For example, the soil types of Western Europe are, by nature, relatively stable, and climatic conditions are not conducive either to wind or water erosion. But the practices of Western Europe, applied in parts of the United States, have resulted in disastrous erosion.

The resistance of farmers to the introduction of new methods—which is, indeed, one of the obstacles to progress—has, upon occasion, proved to be a blessing. Thus, in the early days of soil science there was over-emphasis upon the plant-nutrient aspect of soil fertility. The early Rothamsted work was interpreted by some as implying that the soil could be regarded merely as a reservoir of nitrogen, phosphate, potash, &c., so that, if the farmer would only replace the nutrients removed by his crops, fertility would be maintained. But the matter was not so simple. Soil moisture and soil air, and hence soil structure, are highly important in relation to plant growth; and obviously any system of crop production will fail if the top soil is removed by moving water or by wind.

How far have we progressed in our understanding of the problem? The list of essential plant nutrients is probably complete; the chemist can produce a solution of pure salts, in distilled water, that will support normal plant growth; and we have no evidence that the plant products, when fed to experimental animals, are in any way deficient in nutrient properties.

It has also been shown how any harmful amount of erosion can be prevented. Partly, this is a matter of land-use planning—allocating land to forest, pasture or tillage according to the degree of stability of the soil. Partly, again, in relation to water erosion, it is a matter of applying such techniques as contour ploughing, broad-base terracing and other mechanical operations. Partly it is a matter of growing "cover crops" in the rainy season, to protect the soil surface from the impact of raindrops; and in part it is a matter of maintaining a soil structure that will enable the rain to run in rather than run off.

As I have said, soil structure is important quite apart from the risk of erosion. Plant growth depends not only on nutrients, but also on a reasonably constant supply of water. Again, root activity demands a supply of oxygen and is inhibited by a relatively low concentration of carbon dioxide. Thus, water-holding capacity must be maintained, and aeration must be provided for. These requirements imply the maintenance of crumb structure—a state in which "mellow" crumbs, which act like little sponges, are separated by small channels through which air can penetrate.

If, then, we have a mild binding agent in the soil, if we carry out our tillage operations when the soil has an appropriate moisture content, and if we so arrange our operations as to allow frost and thaw to play their part, we shall achieve the desired condition.

What binding agent can we use? The natural one consists of the colloidal decomposition products of organic matter. These products are unstable, and hence fairly frequent application of organic materials is required.

What forms of organic matter can we use? There is a considerable choice.

First, there is partially decayed plant material, mixed, in many cases, with animal excreta—farmyard manure, compost, and the like.

Second is undecayed organic matter. But here we must ensure that decomposition will proceed at something like the desired rate. This rate depends, in the main, on the ratio of carbon to nitrogen compounds. Thus, cereal straw decays too slowly; green clover decays, under most conditions, too fast. A predominantly grassy sward decays at a rate which may often be near optimum. Moreover, it appears that living or undecayed grass roots have a specific crumb-forming action.

It has recently been shown that certain synthetic plastics are very effective in stabilizing an existing crumb structure, and some of these materials are already available commercially. The immediate obstacle to their general use is their high cost.

Another fact is that the farmer's problem of securing and maintaining soil structure depends on the nature of the soil minerals. Sand, as is well known, is liable to wind erosion when dry, and has little power of holding water. Clay, on the other hand, has a high content of strongly colloidal material and is therefore very sticky when wet and binds, on drying, into hard clods. Loams and silts, with a mixture of sand, clay and intermediate fractions, present the farmer with an easy problem. In the past, sandy soils have been improved by applying clay and marl. A revival of this old practice may be made possible by the development of mechanical equipment, and the operation has lately been included in the list for which State subsidies are available. In some cases, where sand overlies clay—or vice versa—it is possible to achieve a great improvement by deep ploughing. Modern power-drawn ploughs can operate to depths of three feet or more.

Sewage sludge, preferably composted with straw, is a useful source of organic matter, and the only obstacle to its wider use is the cost of transport and handling.

More research is required on the use of the ley as a means to the production of a porous structure. Present indications are that the balance between the grass and clover components is one point of importance, and another may be the management during the last few months before ploughing; the object would seem to be the promotion, at this time, of strong root growth.

Probably, too, a good deal more remains to be discovered about green manuring, i.e. the production of a crop to be ploughed in with the sole object of ameliorating soil structure. In general, the legumes would seem to be relatively inefficient for this purpose, since their residues decay too fast. Probably the best known are quick-growing grasses, with very heavy seedings and high applications of fertilizers.